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TRANSMITTAL OF APPEAL BRIEF (Small Entity)

Docket No.: S&B-C161/wfs

In Re Application Of: **NANA K. AYISI**

Application No.	Filing Date	Examiner	Customer No.	Group Art Unit	Confirmation No.
09/978,593	10/18/01	Ulrike Winkler	30132	1648	5237

Invention: **ANTIVIRAL AND ANTIBACTERIAL ACTIVITIES OF EXTRACTS FROM EIGHT PLANTS**

COMMISSIONER FOR PATENTS:

Transmitted herewith in triplicate is the Appeal Brief in this application, with respect to the Notice of Appeal filed on:

AUGUST 19, 2005

☒ Applicant claims small entity status. See 37 CFR 1.27

The fee for filing this Appeal Brief is: **$250.00**

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Dated: **August 25, 2005**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 09/978,593	Confirmation No.	5237
Applicant	: Nana K. Ayisi		
Filed	: October 18, 2001		
TC/A.U.	: 1648		
Examiner	: Ulrike Winkler		
Docket No.	: S&B-C161		
Customer No.	: 30132		

APPELLANT'S BRIEF UNDER 37 C.F.R. 1.192

Commissioner for Patents
Alexandria, VA 22313-1450
U.S.A.

Dear Sir:

The following is the Appellant's Brief, submitted in triplicate and under the provisions of 37 C.F.R. 1.192.

TABLE OF CONTENTS

TABLE OF CONTENTS – CONT'D

I. Real Party in Interest

The real party in interest in the application is the Applicant.

II. Related Appeals and Interferences

There are no related appeals and interferences.

III. Status of Claims

Claims 1 to 19, 21 and 23 to 30 are cancelled in the application.

Claims 20, 22, 31 and 32 are rejected.

IV. Status of Amendments

No amendments have been made subsequent to the final action of April 19, 2005.

V. Summary of Claimed Subject Matter

The invention is directed to novel methods of inhibiting the cytopathic effects of a virus in a virus-infected cell by contacting the cell with an effective amount of an extract from *Ocimum gratissimum*.

VI. Grounds of Rejection to be Reviewed on Appeal

1. Whether claims 22, 22, 31 and 32 satisfy 35 U.S.C. §112, first paragraph.

2. Whether claims 20 and 31 are unpatentable under 35 U.S.C. §102(b) in view of El-Said *et al.* (Planta Medicine, 1969), as evidenced by the Merck Manual (Ed. Beers *et al.*, Published by

Merck Research Laboratories, Whitehouse Station, N.J. (1999) pp. 1293-1296, 1303-1306, 1312-1323, 2320-2324 and 2341-2343).

VII. Argument

Issue 1. - 35 USC §112, 1st paragraph

The Examiner contends that the specification does not provide enablement for the *Ocimum gratissimum* extract to inhibit the cytopathic effects of a virus in a cell. The Examiner focuses on HIV viral replication as a particular embodiment of the invention to support her position stating in the Office Action dated August 9, 2004:

> The specification does not provide sufficient guidance for the inhibition of a HIV viral infection in a patient with a *O. gratissimum*. There is not [sic] indication that high enough concentrations of the compound can be achieved in the patient to effect [sic] the viral replication *in vivo*. It is not a straightforward process to go from *in vitro* data to an *in vivo* treatment. Thus, the lack of working examples regarding treatment of HIV infection in a patient, the lack of guidance in the specification, and the unpredictability regarding extrapolating *in vitro* data to an *in vivo* treatment method greatly reduces the probability that one of skill in the art would successfully obtain the claimed invention without undue experimentation.

Applicant respectfully disagrees.

(i) Therapeutic Effect of Ocimum Gratissimum Extract

The Examiner firstly argues that there is no indication that high enough concentrations of the compound can be achieved in the patient to affect viral replication *in vivo*.

The objective of the pharmaceutical research undertaken by the Applicant was to establish whether certain plant extracts have a particular pharmacological activity or practical utility, i.e. to inhibit the cytopathic effects of a virus-infected cell as claimed. The Examiner, however, has rejected the claims on the grounds that the teachings of the description give no indication that the *Ocimum gratissimum* extract exhibits a therapeutic effect in a patient. On this basis, Applicant submits that the Examiner's analysis is improper. As held by the court in *In re Borkowski* (422 F.2d 904, 909, 164 USPQ 642, 645 (CCPA 1970)), it is inappropriate "to study appellants' disclosure, to formulate a conclusion as to what he (the examiner) regards as the broadest invention supported by the disclosure, and then to determine whether appellants' claims are broader than the examiner's conception of what 'the invention' is".

Further, it is not necessary to specify concentrations high enough to inhibit viral replication *in vivo* if such information could be obtained by a skilled person without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate concentration without undue experimentation, this would be sufficient to satisfy 35 U.S.C. §112, first paragraph. The courts have recognized that determining an effective concentration for a pharmaceutical agent against a particular disease is well within the ordinary skill in the art, *In re Bundy* (209 U.S.P.Q. 48 (C.C.P.A. 1981)). Based on the disclosure of the instant invention and the state of the art, those skilled in the art had available, at the critical date, information as to approximate concentration levels for the plant extracts to inhibit the cytopathic effect of a virus-infected cell. The *in vitro* data provides sufficient information as an initial starting point so that one skilled in the art could determine, without inventive skill or undue experimentation, the necessary strength or concentrations of the plant extracts to achieve the desired pharmacological effect *in vivo*, i.e., the inhibition of HIV replication in mammalian or human cells. Moreover, a skilled worker would be able to determine the relative strength or concentration of the plant extracts needed to achieve the pharmacological activity, i.e. to inhibit the cytopathic effects of a virus-infected cell, *in vivo* without undue burden or experimentation. The state of the art at the time the application was filed demonstrates the predictability and certainty of practicing the method with particular cell types, particularly with mammalian cells.

(ii) Correlation of In Vitro Testing to In Vivo Efficacy

The Examiner further argues that it is not a straightforward process to go from *in vitro* data to an *in vivo* treatment. Further, while acknowledging that the spescification is enabling for inhibiting HIV viral replication in Vero cells and in Molt4 clone 8 cells with an extract of *Ocimum grattissimum*, the Examiner objects that it does not however, reasonably provide enablement for the *Ocimum grattissimum* extract to inhibit HIV viral replication in a mammalian or other cell line.

The Examiner gives reasons to support her position based on the disclosure of Sandstrom *et al.* (*Antiviral Therapy in AIDS: Clinical and pharmacological properties and therapeutic experience to date.* Drugs (1987) 34:372-390). Sandstrom *et al.* is a review article published in 1987 concerning anti-viral therapy in AIDS which had investigated *in vitro* testing of anti-viral compounds followed by the then available results from clinical testing. This reference discloses that in 1987, those skilled in this art did not associate successful *in vitro* treatment of HIV infected human cells with any probability of achieving success in *in vivo* treatment of this disease. The conclusion as to whether a specific anti-viral compound will be useful *in vivo* based on *in vitro* testing was determined by Sandstrom only from results for the anti-viral compounds suramin and AZT. In discussing suramin as an anti-viral compound in AIDS therapy, Sandstrom states that the high protein binding of this compound "makes predictions from *in vitro* experiments difficult". (See section "1.2.1 Suramin" at pages 375 to 376.) The reference further discloses the results of clinical trials using suramin which discouraged further consideration of this compound as a single-drug treatment modality. Sandstrom also reports the most noted success story in anti-viral therapy in AIDS using AZT. In reporting these results, Sandstrom does not disclose that the *in vitro* testing of AZT provided any basis for concluding that this anti-viral compound would, in fact, be useful in *in vivo* therapy. Sandstrom's comments are thus restricted to two specific anti-viral compounds that are unrelated to an extract of *Ocimum grattissimum*.

Applicant respectfully disagrees and finds the Examiner's reliance on the teachings of Sandstrom to be misplaced. The difficulty in concluding whether *in vitro* testing is predictive of *in vivo* efficacy was determined solely on the basis of results for suramin and AZT. For example, Sandstrom *et al.* describes problems which are specific to the particular properties of some anti-viral compounds, such as suramin which, in absence of evidence to the contrary, are not relevant to the extract from *Ocimum gratissimum.*

The majority of known anti-viral drugs are nucleoside analogs that exert their effects through an enzyme involved in producing new copies of the viral genetic material, such as a nucleoside kinase or a polymerase or reverse transcriptase or replicase. These analogs are typically metabolized into nucleotide analogs that inhibit production of viral nucleic acid, for example by inhibiting a polymerase or by causing premature chain termination of growing viral nucleic acids. However, because viral and cellular nucleic acid metabolism are so similar, it would have been difficult at that time to find anti-viral agents that are not used to some extent by host cell enzymes. Thus, the mode of action exerted by these compounds on viral replication may detract from any level of predictability that can be made from *in vitro* results to *in vivo* efficacy.

Further, as Sandstrom *et al.* was published in 1987, Applicant submits that the reference is not relevant to the state of the rapidly developing HIV art as of the filing date of the instant application 10 years later (i.e. 09 Dec 1997). Advances made subsequent to 1987 in the knowledge of the molecular details of virion structures and viral replication have increased our understanding of the role of specific viral proteins in HIV infection and disease. Further, numerous studies involving viral replication, pathogenesis, and host interaction pathways have not only contributed towards our basic understanding of the HIV life-cycle, but they have also provided us with novel targets for more selective antiviral agents and therapeutic intervention. In light of advances made over the last 10 years after Sandstrom, Applicant respectfully submits that Sandstrom does not provide an accurate representation of the state of the art as at the filing date of the instant application and doubts whether a skilled person would find it reliable.

(iii) Working Examples and Guidance in the Specification

Applicant further submits that the Examiner's dismissal of an *in vitro* model as a working example for the method as claimed is inconsistent with U.S. patent practice and law. For example, MPEP Section 2164.02 provides that:

> An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples". In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications). [Emphasis added.]
>
> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985).

Successful *in vitro* testing for a particular pharmacological activity, as in the instant case, establishes a significant probability that *in vivo* testing for the same pharmacological activity will likely be successful. The exemplified cell lines "Vero" and "Molt-4 clone 8" are well known and art-accepted model systems that provide characteristics suitable for testing the ability of the plant extracts to inhibit HIV production in chronically infected cells, thereby reducing HIV

cytopathicity. (See also, for example, U.S. Patent No. 6,685,950, "Methods of Treating Viral Infections".) It is not urged that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (1980).

(iv) Predictability of In Vitro Data to In Vivo Test Results

It is Applicant's further position that successful *in vitro* testing for a particular inhibitory/therapeutic activity in an accepted model establishes a significant probability that *in vivo* testing for this particular activity will be successful *in vivo*. It is well established under U.S. patent law and practice that *in vitro* results with respect to the particular pharmacological activity can be predictive of *in vivo* test results, if there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (1980).

For example, research conducted prior to the filing date of the instant application has shown that *in vitro* models can be predictive of the clinical situation in combination therapy that was examined for its potential in the treatment of HIV[1,2,3]. These published studies further confirm that advances made in research have contributed to our understanding of HIV viral replication. In particular, it is now recognized that *in vitro* data must be interpreted more carefully and considered in light of other controlling factors in order to correlate it effectively to *in vivo* efficacy.

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[1] Patrick G. Hoggard *et al. Effects of Drugs on 2',3'-Dideoxy-2',3'-Didehydrothymidine Phosphorylation In Vitro.* Antimicrobial Agents and Chemotherapy (1997) 1231-1236.

[2] Diane V. Havlir *et al. In Vivo Antagonism with Zidovudine plus Stavudine Combination Therapy.* The Journal of Infectious Diseases (2000); 182:321-325.

[3] Robert W. King *et al. Potency of Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs) Used in Combination with Other Human Immunodeficiency Virus NNRTIs, NRTIs, or Protease Inhibitors.* Antimicrobial Agents and Chemotherapy (2002) 1640-164.

In addition, scientific knowledge acquired through research and which has contributed to the state of the art in the course of 10 years has likely led to the design and development of *in vitro* tests that better correlate to the *in vivo* performance of drug products.

Further, Applicant's post-filing publication[4] comparing the effects of *Ocimum gratissimum* (and other plant extracts) to AZT on *in vitro* HIV-1 and HIV-2 replication and cytopathicity supports the ability of these compounds to be effective *in vivo*. Using AZT as a point of reference, in light of its relative acceptance and success as a viral inhibitor in AIDS therapy, the results support the therapeutic potential of the anti-viral plant extracts. Applicant wishes to emphasize that its intention is not to rely its post-filing published results to add to the knowledge of the disclosure. Indeed, the instant application is written to enable those skilled in the art to practice the invention as of the application filing date. Rather, Applicant believes that the publication provides further credible evidence that those persons skilled in this art would equate *in vitro* activity of anti-viral compounds described in the present specification with *in vivo* efficacy in inhibiting viral replication in cells. These findings show that *Ocimum gratissimum* (and other plant extracts) was effective in HIV inhibition irrespective of the multiplicity of infection examined when compared to AZT. The encouraging results of this study are attributed to the different mode of action exerted by these compounds compared to AZT, and their ability to inhibit viral replication at different stages of HIV replication (e.g. early as opposed to late viral events). Thus, Applicant respectfully submits that *in vitro* testing of *Ocimum gratissimum* set forth in the instant specification (and illustrated by Applicant's post-filing publication) would be accepted by those skilled in the art as a basis for concluding that this compound would be useful in inhibition of viral replication *in vivo*.

(v) Enablement

The Examiner concludes that based on (1) the lack of working examples regarding treatment of HIV infection in a patient, (2) the lack of guidance in the specification, and (3) the

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[4] Nana K. Ayisi *et al. Comparative in vitro effects of AZT and extracts of Ocimum gratissimum, Ficus polita, Clausena anisata, Alchornea cordifolia, and Elaeophorbia drupifera against HIV-1 and HIV-2 infections.* Antiviral Research (2003) 58:25-33. (Copy enclosed.)

unpredictability regarding extrapolating *in vitro* data to an *in vivo* treatment method, the probability that one of skill in the art would successfully obtain the claimed invention without undue experimentation is greatly reduced.

The enablement section of 35 U.S.C. §112, first paragraph, "requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re Fisher* (427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)). To that end, the court in *In re Marzocchi* (439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)) directs one to consider that "a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of 35 U.S.C. §112 unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

Further, it is well established under 35 U.S.C. §112 that for a specification to be enabling, it must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation". *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988)); *In re Fisher* (427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)) (the first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification). Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. *In re Marzocchi* (439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)).

In Applicant's opinion, the Examiner's analysis of the enablement requirement is incomplete and has focused almost exclusively on, and given undue weight to, statements of unpredictability in the art, to support the inability of the *in vitro* model employed by the Applicant to be correlated to *in vivo* results. It is true that unpredictability is a factor to be considered. However, it would appear that the Examiner has not properly considered the state of the art in formulating her

assessment of the enablement issue. While the factors relied on by the examiner are relevant in determining whether the claimed invention is enabled by the specification, on balance, they are insufficient, in view of the state of the art, to establish a reasonable basis to doubt the objective truth of statements, experiments and examples provided in the specification.

A clear goal is disclosed in the instant application; i.e, to inhibit the cytopathic effects of a virus-infected cell using an extract from *Ocimum gratissimum*. Examples are provided which describe the techniques necessary to make and practice the novel methods. While the specification focuses on Vero and Molt4 clone 8 cells, there is no evidence that the methods detailed therein are not a sufficient guide for one of skill in the art to apply the same techniques to other mammalian cells. Whatever unpredictability surrounds the use of cells other than the Vero and Molt4 clone 8 cells, the need for undue experimentation is alleviated by Applicant's clearly described examples of how to make and use the claimed methods. There is no evidence that the invention exemplified therein would not find equal application in numerous other embodiments. The lack of evidence of undue experimentation as to these other embodiments cannot be replaced by speculating about the possibility of producing an inoperative result. In other words, the Examiner has not articulated any reasons as to why one of skill in the art would have been unable to perform the claimed method other than to rely on the "unpredictability" of *in vitro* testing to correlate to *in vivo* efficacy.

In summary, it is submitted that the disclosure satisfies the enablement requirement of 35 USC §112, first paragraph since (1) working examples regarding the pharmacological activity of the plants extracts to inhibit the cytopathic effects of a virus-infected cells are provided, (2) adequate guidance to practice the invention is provided in the specification, and (3) the extrapolation of *in vitro* data to an *in vivo* method of use using art-accepted cell lines provides a significant probability that one of skill in the art would successfully obtain the invention as claimed without undue experimentation. Accordingly, Applicant respectfully submits that the Examiner has not met her burden of establishing a *prima facie* case of non-enablement and requests that the rejection be withdrawn.

Issue 2. - 35 USC §102(b)

The Examiner has reapplied El-Said *et al.* as anticipating the claimed subject matter on the grounds that the instant invention reads on the treatment of a viral infection *in vivo* using an extract of *Ocimum gratissimum*. Further evidence in support of the Examiner's rejection is provided by the Merck Manual (Ed. Beers *et al.*, Published by Merck Resarch Laboratories, Whitehouse Station, J.J. (1999) pages 1293 to 1296, 1303 to 1306, 1312 to 1323, 2320 to 2324 and 2341 to 2343). The Merck Manual shows that fever is a symptom associated with viral or bacterial infections. The Examiner contends that because El-Said *et al.* disclose the use of an extract of *Ocimum gratissimum* for the treatment of fevers, the prior art method inherently would achieve whatever desired outcome was discovered and claimed by the Applicant.

F. El-Said *et al.* disclose the chemotaxonomy and **antibacterial** testing of *Ocimum gratissimum* specimens collected from different areas around Ibadan, Western State of Nigeria. *Ocimum gratissimum* is known for its medicinal properties in the treatment of fever, as a diaphoretic, a stomachic and laxative.

At page 197, the authors describe the preparation and testing of (a) an aqueous extract of the whole plant, (b) the essential oil, and (c) an aqueous solution of the oil for their ability to inhibit growth of certain gram-negative and gram-positive bacterial organisms, including:

Gram-Negative		Gram-Positive
Escherichia coli	*Salmonella spp.*	*Bacillus subtilis*
Klebsiella aerogenes	*Shigella schmitzi*	*Sarcina lutea*
Proteus spp.	*Shigella sonnei*	*Staphylococcus aureus*
Pseudomonas aeruginosa		

Cultures of the various organisms were spread across a petri dish containing nutrient agar. The aqueous extract was contained in a "ditch" that was formed in the center of the agar. The essential oil was tested by placing small drops on the surface of the seeded agar plates. Aqueous dilutions of the oil were made in nutrient broth and innoculated with broth culture of the particular organism.

In contrast, the instant specification discloses the testing of plant extracts against viruses, such as HIV, herpes virus, and others that afflict mankind (see, for example, page 2, lines 26 to 31).

Applicant submits that the Examiner's rejection is inconsistent with U.S. patent law and practice, and refers to MPEP §2131 which provides that:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference." *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The **identical invention** must be shown in as complete detail as contained in the ... claim." [Emphasis added.] *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim.

Further, MPEP §2121.01 provides that:

> "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel'or 'anticipated' within section 102, the stated test is whether a reference contains an **'enabling disclosure'** ... ." *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). [Emphasis added.] A reference contains an enabling disclosure if the public was in possession of the claimed invention before the date of the invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985).

The invention, as claimed, is not anticipated by F. El-Said *et al.* because the reference does not disclose anti-viral testing and/or a method of use of *Ocimum gratissimum* for inhibiting the cytopathic effects of a virus-infected cell. Bacteria are single-celled organisms, capable of reproducing on their own whereas a virus is an infectious agent, smaller than bacteria, which

requires the cells of a living organism in order to grow or reproduce. Thus, a bacteria is self-sufficient whereas a virus is not self-sufficient. Not surprisingly, because bacteria and viruses are different in composition, their mode of infection and underlying pathology in causing various diseases are also vastly different.

However, the Examiner argues that because fever is a symptom that is associated with both viral and bacterial infections, the treatment of viral infection using an extract of *Ocimum gratissimum* is anticipated by El-Said *et al.* Applicant respectfully submits that the Examiner's rejection is unfounded.

Both viral and bacterial infections share many of the same symptoms. However, while it may be that the symptoms of a bacterial and viral infection are fairly similar, it is for this reason that the initial step to treating any bacterial or viral infection is to distinguish one from the other. Blood tests and bacterial cultures help distinguish between bacterial and viral infections. For example, if a blood test indicates increased white blood cell count, it is indicative of a bacterial infection. A bacterial culture will further aid in determining the type of bacterial infection. In contrast, a blood test showing a decreased white blood cell count is indicative of a viral infection.

Further, the distinction between viruses and bacteria is important because drugs that are effective against one type of infection won't work against the other type. Antibiotics treat pathogenic bacterial infections, however, they cannot effectively treat viral infections. Further, unlike antibiotics used to treat bacterial infections, there is no specific class of drugs that treat viral infections such as influenza and the common cold. Also, administering antibacterial antibiotics to a patient who may have a viral infection can be harmful.

Accordingly, Applicant submits that El-Said *et al.* does not anticipate a method of inhibiting the cytopathic effects of a virus-infected cell using an *Ocimum gratissimum* extract, either explicitly or inherently. With respect to inherent anticipation, Applicant refers to the decision in *In re Marshall* (578 F.2d 301, 198 USPQ 344 (CCPA 1978).

In re Marshall, the claims at issue were directed to a process for achieving weight loss by periodically administering an anesthetic prior to eating to inhibit the release of hormones and preventing the subsequent release of pancreatic enzymes that would otherwise digest food passing through the digestive tract. The following dependent claim was directed to the anesthetic oxethazaine: "A weight control process as claimed in claim 2 wherein said anesthetic means is oxethazaine." The cited prior art was the Physician's Desk Reference (PDR) which prescribed oxethazaine to treat colitis, ulcers and other types of gastrointestinal disorders by dosing periodically prior to eating and at bedtime. The PDR also disclosed that this anesthetic inhibited release of the acid-stimulating hormone, gastrin. The CCPA held that the PDR did not disclose every material element of the claimed subject matter because the claims were directed to a weight control process and nothing in the PDR remotely suggested taking oxethazaine to lose weight. Accordingly, the court held that no anticipation was found stating:

> Nothing in the PDR remotely suggests taking oxethazaine to lose weight. If anyone ever lost weight by following the PDR teachings, it was an unrecognized accident. An accidental or unwitting duplication of an invention cannot constitute an anticipation.

Accordingly, Applicant respectfully submits that the invention, as claimed, is novel over the prior art and requests that the rejection be withdrawn.

Relief Requested

In view of the foregoing, the Applicant requests that the appeal be allowed.

Respectfully submitted,

NANA K. AYISI

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Date: August 25, 2005
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Listing of Claims:

Claim 19 (Canceled)

20 (Currently amended) The method according to claim ~~19~~ 31, wherein the virus is human immunodeficiency virus (HIV), herpes simplex virus (HSV), human cytomegalovirus (HCMV), poliovirus (PV), measles virus (MV) or yellow fever virus (YMV).

21 (Canceled)

22 (Currently amended) The method according to claim ~~21~~ 20, wherein the virus is HIV-1, HCMV, HSV-1 or HSV-2.

Claims 23 through 30 (Canceled)

31 (New) A method comprising: contacting a virus-infected cell with an extract from *Ocimum gratissimum* in an amount effective to inhibit cytopathic effects of the virus in the cell.

32 (New) The method according to claim 20, wherein the virus is HIV.

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With this edition, *Th*
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MARK

ction with several different adenovirus se-
types. It occurs most often in young adults,
iefly parents of children with APC, and is
lf-limited and benign. Onset is sudden and
ually unilateral. Symptoms and signs in-
ude a foreign-body sensation in the eye,
crimation, and focal erythema of the pal-
bral and bulbar conjunctiva. The dis-
arge is mucoid but not purulent. In about
lf the patients, the other eye is subse-
ently involved, usually less severely. Per-
stent follicular enlargement of submucous
mphoid tissue under the palpebral con-
nctiva, even resembling early trachoma,
ay be seen about 2 to 4 days after onset.
eauricular and posterior cervical lymph-
lenopathy, more prominent on the same
de as the more involved eye, is usual. A mild
re throat occasionally develops, often on
e same side as the affected eye. The course
mild, although focal conjunctival hemor-
ages and periorbital edema occur occa-
onally.

Epidemic keratoconjunctivitis (EKC) a specific, sometimes severe, epidemic dis-se caused by adenoviruses. Observed for any years in Japan, it became epidemic in e USA during World War II, chiefly among ipyard workers on both coasts. It has oc-rred only sporadically in this country since en, but widespread epidemics have oc-rred in Europe and Asia. Onset is sudden; ie eye shows redness and chemosis fol-wed by periorbital swelling, preauricular mphadenopathy, and superficial corneal pacities. Unlike herpetic keratitis, it does ot result in corneal ulceration; however, lo-l pain like that from foreign-body irritation usual. The other eye may become involved thin a week. Systemic symptoms and signs e mild or absent. EKC usually resolves thin 3 or 4 wk, although corneal opacities ay persist much longer, and vision may be rmanently impaired.

Autopsies have disclosed microscopically nique, extensive inclusion body pneumo-a; the intranuclear inclusions appear simi-to those seen in tissue cultures. Biopsies superficial lesions produced by adenovi-ses in conjunctival and pharyngeal mu-sa show capillary dilatation, occasional omucous hemorrhage, and mononuclear kocyte infiltration but no intranuclear in-sions. The conjunctivitis caused by the mmon respiratory adenovirus types is usu-/ benign, but sometimes keratoconjunc-tivitis (as is caused by type 8) with corneal opacities and impaired vision occurs.

Diagnosis

Clinical identification of adenoviral infection is only presumptive, except in epidemics of APC, EKC, and ARD; in these conditions, the clinical or epidemiologic characteristics or both are unmistakable. During the acute stages of adenoviral illnesses, the virus can be isolated for 7 to 10 days from respiratory and ocular secretions and frequently from feces and urine, although this is rarely done except for epidemiologic indications. A four-fold rise in the serum antibody titer indicates recent adenoviral infection.

Prognosis and Prophylaxis

Adenoviral infections are generally benign and are relatively short-lived. Except for rare cases of fulminating primary pneumonia, predominantly in infants and military recruits, even severe adenoviral pneumonia is not fatal.

Vaccines containing live adenovirus types 4 and 7, given orally in an enteric-coated capsule, have markedly reduced ARD in military populations; however, they are neither recommended nor available for civilian use. Spread of virus through vaccines is possible but is inconsequential. Vaccines for a few other serotypes have been developed but are not commercially available.

Washing is critical since, among civilians, adenoviruses causing outbreaks of conjunctivitis are spread by contact with contaminated objects (eg, towels, instruments), by secretions, or by finger transmission. Practicing proper sterilization techniques, changing gloves and washing hands before and after examining infected patients, and avoiding multiple patient exposures to ophthalmologic instruments are recommended to prevent transfer of virus by healthy persons.

Treatment

Treatment is symptomatic and supportive. Bed rest may be required during the acute febrile period. Aspirin is not recommended unless headache and malaise are distressing; for children, acetaminophen may be preferred because of concerns of Reye's syndrome; analgesics such as codeine are rarely necessary. Severe pneumonia in infants and EKC require close supervision to prevent death in the former and permanently impaired vision in the latter. Topical corticosteroids relieve symptoms and shorten the course of EKC and adenoviral conjunctivitis. Such therapy is dangerous in ulcerative corneal conditions, however, and should always be supervised by an ophthalmologist.

HERPESVIRUS INFECTIONS

HERPES SIMPLEX

An infection with herpes simplex virus characterized by one or many clusters of small vesicles filled with clear fluid on slightly raised inflammatory bases.

Etiology

The two types of herpes simplex virus (HSV) are HSV-1 and HSV-2. HSV-1 commonly causes herpes labialis, herpetic stomatitis, and keratitis; HSV-2 usually causes genital herpes, is transmitted primarily by direct (usually sexual) contact with lesions, and results in skin lesions. (Genital herpes is discussed in Ch. 164, herpes simplex keratitis in Ch. 96, and primary and recurrent herpetic stomatitis in Ch. 105.)

The time of initial HSV infection is often obscure. After initial eruption, HSV remains dormant in the nerve ganglia. Recurrent herpetic eruptions can occur, precipitated by overexposure to sunlight, febrile illnesses, physical or emotional stress, or immunosuppression. The trigger stimulus is often unknown. Recurrent disease is generally less severe than primary disease.

Symptoms and Signs

The lesions may appear anywhere on the skin or mucosa but are most frequent around the mouth, on the lips, on the conjunctiva and cornea, and on the genitalia. After a prodromal period (generally < 6 h in recurrent HSV-1) of tingling discomfort or itching, small tense vesicles appear on an erythematous base. Single clusters vary in size from 0.5 to 1.5 cm, but groups may coalesce. Skin lesions involving the nose, ears, or fingers may be particularly painful. The vesicles persist for a few days, then begin to dry, forming a thin yellowish crust. Healing generally occurs in 8 to 12 days after onset. Individual

herpetic lesions usually heal completely, but recurrent lesions at the same site may cause atrophy and scarring.

Primary infection of HSV-1 typically causes a gingivostomatitis, which is most common in infants and young children. Symptoms include irritability, anorexia, fever, gingival inflammation, and painful ulcers of the mouth.

Primary infection of HSV-2 typically occurs on the vulva and vagina or penis in young adults. Illness is accompanied by fever, malaise, and tender inguinal adenopathy. HSV-2 infection may occur in newborns and cause severe disseminated disease (see NEONATAL HERPES SIMPLEX VIRUS INFECTION under NEONATAL INFECTIONS in Ch. 260).

HSV occasionally causes severe encephalitis (see ACUTE VIRAL ENCEPHALITIS AND ASEPTIC MENINGITIS in Ch. 176). HSV-2 has also been associated with usually self-limited aseptic meningitis and lumbosacral myeloradiculitis syndromes, which may include urinary retention or obstipation.

In patients with AIDS, herpetic infections can be particularly severe. Progressive and persistent esophagitis, colitis, perianal ulcers, pneumonia, and neurologic syndromes may occur.

HSV outbreaks may be followed by typical erythema multiforme. Eczema herpeticum is a complication of HSV infection in which patients have severe disease in skin regions with eczema.

Herpetic whitlow, a swollen, painful, and erythematous lesion of the distal phalanx, results from inoculation of HSV through a cutaneous break or abrasion and is most common in health care workers.

Diagnosis

Diagnosis is confirmed by cultures for the virus, seroconversion and a progressive increase in serum antibodies to the appropriate serotype (in primary infections), and biopsy findings. A Tzanck preparation of the base of a lesion often reveals multinucleate giant cells in HSV or varicella-zoster virus infection. Newer techniques such as the polymerase chain reaction of CSF may allow early noninvasive diagnosis of herpes simplex encephalitis.

HSV should be distinguished from herpes zoster, which rarely recurs and usually causes more severe pain and larger groups of lesions distributed along a dermatome. Differential diagnosis includes varicella, genital ulcers or gingivostomatitis due to other causes, and vesicular dermatoses, particularly dermatitis herpetiformis and drug eruptions.

Treatment

Systemic treatment with acyclovir is used in serious herpes infections, such as disseminated neonatal disease, in herpes simplex encephalitis, and in immunocompromised patients. Acyclovir, valacyclovir, and famciclovir can each be used for suppression of recurrent eruptions. Under the supervision of an ophthalmologist, topical trifluridine is used to treat herpes simplex keratitis. Topical penciclovir can be used to treat recurrent orolabial HSV and topical acyclovir for initial herpes genitalis. IV foscarnet is used for HSV (mucocutaneous) resistant to acyclovir in immunosuppressed patients. Acyclovir, valacyclovir, and famciclovir dosages are discussed in Ch. 154.

Secondary infections are treated with topical antibiotics (eg, neomycin-bacitracin ointment) or, if severe, with systemic antibiotics.

HERPES ZOSTER

(Shingles; Zona; Acute Posterior Ganglionitis)

An infection with varicella-zoster virus primarily involving the dorsal root ganglia and characterized by vesicular eruption and neuralgic pain in the dermatome of the affected root ganglia.

Etiology, Incidence, and Pathology

Herpes zoster is caused by varicella-zoster virus, the same virus that causes chickenpox (see Ch. 265). Herpes zoster occurs when the virus is reactivated from its latent state in the posterior root ganglia. Inflammatory changes occur in the sensory root ganglia and in the skin of the associated dermatome. The inflammation sometimes involves the posterior and anterior horns of the gray matter, the meninges, and the dorsal and ventral roots. Herpes zoster frequently occurs in HIV-infected patients and is more severe in immunosuppressed patients.

Symptoms and Signs

Pain along the site of the future eruption usually precedes the rash by 2 to 3 days.

Differential diagnosis includes varicella, genital ulcers or gingivostomatitis due to other causes, and vesicular dermatoses, particularly dermatitis herpetiformis and drug eruptions.

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Symptoms and Signs

Pain along the site of the future eruption usually precedes the rash by 2 to 3 days. Characteristic crops of vesicles on an erythematous base then appear, following the cutaneous distribution of one or more adjacent dermatomes. The involved zone is usually hyperesthetic, and pain may be severe. Eruptions occur most often in the thoracic or lumbar region and are unilateral. Lesions usually continue to form for about 3 to 5 days. Herpes zoster may disseminate to other regions of the skin and to visceral organs, especially in immunosuppressed patients.

Fewer than 4% of patients with herpes zoster experience recurrence; most patients recover, but many, particularly the elderly, have postherpetic neuralgia, which may persist for months or years. The pain of postherpetic neuralgia may be sharp and intermittent or constant and may be debilitating.

Geniculate zoster (Ramsay Hunt's syndrome) results from involvement of the geniculate ganglion. Pain in the ear and facial paralysis occur on the involved side. A vesicular eruption occurs in the external auditory canal, and taste may be lost in the anterior two thirds of the tongue (see also HERPES ZOSTER OTICUS in Ch. 85).

Ophthalmic herpes zoster (see also in Ch. 96) follows involvement of the gasserian ganglion, with pain and a vesicular eruption in the distribution of the ophthalmic division of the 5th nerve. Vesicles on the tip of the nose indicate involvement of the nasociliary branch of the 5th nerve and may predict the occurrence of corneal lesions. However, eye involvement may occur in the absence of lesions on the tip of the nose. An ophthalmologist should be consulted to help evaluate and prevent invasive eye disease.

Diagnosis

Diagnosis is difficult in the preeruption stage but is readily made after the vesicles appear. The Tzanck preparation shows multinucleate giant cells for both varicella-zoster virus and HSV. Antigen detection from a biopsy can be useful. Pleurisy, trigeminal neuralgia, Bell's palsy, and chickenpox (in children) must be differentiated. HSV may produce nearly identical zosteriform lesions, but unlike herpes zoster, HSV tends to recur. The viruses can be differentiated serologically and by culture.

Treatment

Locally applied wet compresses are soothing, but analgesics are often necessary.

For immunosuppressed patients with herpes zoster, acyclovir IV is recommended at a dosage of 10 mg/kg q 8 h for 7 days for adults and 500 mg/m^2 q 8 h for 7 days for children ≥ 1 yr (30 mg/kg/day in 3 divided doses for children < 1 yr). Oral famciclovir, valacyclovir, and acyclovir are all used for treatment of herpes zoster in immunocompetent patients, and data indicate they may decrease postherpetic neuralgia as well as accelerate healing. Famciclovir and valacyclovir have better bioavailability with oral dosing than acyclovir.

To try to prevent neuralgia, corticosteroids have been used, but the data are controversial and such treatment is not recommended. Management of postherpetic neuralgia can be particularly difficult and may include tricyclic antidepressants.

For treatment of ophthalmic herpes zoster, see Ch. 96.

CYTOMEGALOVIRUS INFECTION

(Cytomegalic Inclusion Disease)

Various infections caused by cytomegalovirus, occurring congenitally, postnatally, or at any age, ranging from inconsequential silent infection to disease manifested by fever, hepatitis, pneumonitis, and, in newborns, severe brain damage, stillbirth, or perinatal death.

(See also CONGENITAL AND PERINATAL CYTOMEGALOVIRUS INFECTION under NEONATAL INFECTIONS in Ch. 260.)

Etiology and Epidemiology

Transmission of cytomegalovirus (CMV) is through blood, body fluids, or transplanted organs. Infection may be acquired transplacentally or during birth. Cytomegalic inclusion disease refers to the intranuclear inclusions found in enlarged infected cells. Prevalence in the general population increases gradually with age; 60 to 90% of adults have had CMV infection. Lower socioeconomic groups tend to have a higher prevalence.

Symptoms and Signs

Congenital infection may be manifested only by cytomegaloviruria in an otherwise apparently normal infant. At the other extreme, CMV infection may cause abortion, stillbirth, or postnatal death from hemorrhage, anemia, or extensive hepatic or CNS

damage (see CONGENITAL AND PERINATAL CYTOMEGALOVIRUS INFECTION under NEONATAL INFECTIONS in Ch. 260).

Acquired infections are often asymptomatic, whether acquired postnatally or later in life. An acute febrile illness, termed cytomegalovirus mononucleosis or cytomegalovirus hepatitis, may occur.

In immunosuppressed patients, CMV is a major cause of morbidity and mortality. Disease often results from reactivation of latent virus infection. Patients may have pulmonary, GI, or CNS involvement. In the terminal phase of AIDS, CMV infection commonly causes retinitis and ulcerative disease of the colon or esophagus (see Ch. 163).

Postperfusion/posttransfusion syndrome can develop in a normal host 2 to 4 wk after transfusion with fresh blood containing CMV. It is characterized by fever lasting 2 to 3 wk, hepatitis of variable degree, splenomegaly, and a characteristic atypical lymphocytosis resembling that of infectious mononucleosis. Disease generally resembles spontaneous CMV mononucleosis, although splenomegaly is more common.

Diagnosis

Especially in the immunocompromised host, CMV may be isolated from urine, other body fluids, or tissues. However, CMV can be excreted for months or years after infection without causing active disease, and a positive CMV culture must be interpreted with regard to the particular host and disease manifestation. Biopsy showing CMV-induced pathology is often important in demonstrating invasive disease. Promising techniques for rapid diagnosis include demonstrating CMV antigens or DNA.

Congenital infection must be differentiated from bacterial, viral (eg, rubella), and protozoan (eg, toxoplasmosis) infections. Diagnosis in infants is best made by urine culture.

CMV mononucleosis must be differentiated from viral hepatitis, Epstein-Barr virus, and other causes of mononucleosis-like syndromes. The absence of pharyngitis and a negative heterophil antibody test help distinguish primary CMV mononucleosis from Epstein-Barr virus infection, but fever and atypical lymphocytosis are typical of both syndromes. Seroconversion can be demonstrated by development of CMV antibodies.

Treatment

Ganciclovir IV is used to treat CMV retinitis and for prophylaxis of CMV disease in transplant recipients at risk for developing CMV disease. Oral ganciclovir is used for prevention of CMV disease in HIV patients and for maintenance therapy in certain patients with CMV retinitis. Ganciclovir ocular implants provide prolonged treatment for retinitis but do not provide systemic treatment. Foscarnet and cidofovir are also used for CMV retinitis in patients with AIDS. Intraocular injections of ganciclovir or foscarnet have been performed at times, primarily as salvage therapy. Anti-CMV agents are used to treat nonretinitis severe CMV disease, but response to treatment is somewhat less consistent. Passive CMV immune globulin has had some success at reducing disease in certain seronegative transplant recipients (see also Ch. 154). Ganciclovir plus immune globulin has been used to treat CMV pneumonia in bone marrow transplant patients.

CENTRAL NERVOUS SYSTEM VIRAL DISEASES

RABIES

(Hydrophobia)

An acute infectious disease of mammals, especially carnivores, characterized by CNS pathology leading to paralysis and death.

Etiology and Epidemiology

Rabies is caused by a neurotropic virus often present in the saliva of rabid animals. Isolates of rabies virus collected from different animal species and from different parts of the world are distinct.

Rabid animals transmit the infection by biting animals or humans. Rabies is rarely transmitted from infected saliva to a mucous membrane or skin abrasion. Other rare cases of respiratory infections followed exposure in the laboratory and from the atmosphere of a bat-infested cave.

Worldwide, rabid dogs still present the highest risk to humans. Rabies in dogs is prevalent in Latin America, Africa, and Asia. In the USA, where vaccination has largely eliminated canine rabies, bites of infected wild animals, especially bats, have caused most of the infrequent cases of human rabies since 1960.

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Diagnosis

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nts are present, and the patient shows an
ıggerated startle response. Emotional la-
ty is present, with pathologic bursts of
ghter. Dementia may be present in ad-
ıced stages. In a terminal state, the patient
ɡenerally totally placid, mute, and unre-
ınsive. Death usually occurs in 3 to 12 mo
l is caused by severe decubitus ulcers or
ɔostatic pneumonia.
The disease has been transmitted experi-
ntally.

rstmann-Sträussler-Scheinker ɔease

lowly progressive genetic disease that is ıassed as an autosomal dominant trait.

similar to Creutzfeldt-Jakob disease, it is
ısmissible to experimental animals. The
ease is found worldwide; however, the in-
ence is about 100-fold less than Creutz-
lt-Jakob disease. Also in contrast, Gerst-
nn-Sträussler-Scheinker disease has an
lier age of onset (40 vs. 60 yr) and a longer
rage duration of disease (5 yr vs. 9 mo).
Patients appear to have a spinocerebellar
ɡeneration or an olivopontocerebellar de-
ıeration, with cerebellar ataxia occurring
t. Myoclonus is much less common. The
ease progresses to limb ataxia, dysarthria,
tagmus, dementia, parkinsonism, deaf-
s, blindness, and gaze palsies. Eventually
corticospinal tract is involved.

al Familial Insomnia

rapidly progressive genetic disease, ıassed as an autosomal dominant trait.

This very rare disease is associated with
ɔn protein (PrP) and appears to have the
ıe mutations as that of Creutzfeldt-Jakob
ease; however, familial fatal insomnia is
icult to transmit to experimental animals.
ɔccurs in select kindreds that carry the
C-AAC mutation at codon 178 of the prion
ıe. The age of onset varies widely from the
30s to the early 60s; the average age is
yr. Unlike the other spongiform encepha-
pathies, the changes to the gray matter
confined to the thalamic nuclei, resulting
he disruption of the sleep/wake cycle.
n the early stages of the disease, the pa-
ıt may have mild difficulties falling asleep
l intermittent motor difficulties. This
ge can last for months but eventually progresses to insomnia, myoclonus, sympathetic hyperactivity, and dementia. The course of disease averages 13 mo.

ARBOVIRUS AND ARENAVIRUS DISEASES

***Arboviruses** are maintained in nature through transmission between vertebrate and hematophagous arthropod hosts; they multiply in both. **Arenaviruses** belong to the family* Arenaviridae *and are usually transmitted by rodents but sometimes from human to human.*

Arbovirus is an early, ecologically based designation; changes in taxonomy, based on viral morphology, structure, and function, have distributed the arboviruses among several families, most notably the Togaviridae, Flaviviridae, Bunyaviridae, and Reoviridae. Important diseases are listed by clinical syndrome in TABLE 162–6.

The arboviruses (*arthropod-borne* viruses) number > 250; at least 80 immunologically distinct arboviruses cause disease in humans. Arboviruses are transmitted among vertebrates by biting insects, chiefly mosquitoes and ticks. Birds are often sources of infection for mosquitoes, which then transmit the infection to horses, other domestic animals, and humans. Humans are dead-end hosts (ie, incidental to the natural cycle and ineffective in virus perpetuation) for most of the agents, but are definitive hosts (ie, part of the natural cycle and necessary for viral propagation) in urban yellow fever, phlebotomus fever, chikungunya, and dengue. Arboviruses are widely distributed throughout the world, depending on the availability of appropriate hosts and vectors.

IV ribavirin (only aerosol currently approved in USA) (2-g loading dose followed by 1 g q 6 h for 4 days, then 0.5 g q 8 h for 6 days) is effective in Lassa fever, Rift Valley fever, and Crimean-Congo hemorrhagic fever. For dosage in hemorrhagic fever with renal syndrome, see below. Treatment for most arbovirus infections is supportive, as in other viral encephalitides (see in Ch. 176).

Arboviruses cause three syndromes (aseptic meningitis-encephalitis, arthralgia-arthritis, and hemorrhagic disease), minor nonspecific febrile illnesses, and, most commonly, asymptomatic infection.

ARBOVIRUS ENCEPHALITIS

In the USA, **Western equine encephalitis** occurs throughout the country in all age groups, but a disproportionate number of cases involve children < 1 yr. **Eastern equine encephalitis** occurs in the eastern USA, mainly in young children and persons > 55 yr, and has a higher mortality rate than that of Western equine encephalitis. In children < 1 yr, both types tend to be severe, with permanent neurologic sequelae. Epidemics of both types are associated with epizootics in horses.

Urban and rural outbreaks of **St. Louis encephalitis** have occurred throughout the USA; morbidity and mortality are greatest in older age groups. The **California encephalitis virus group** is distributed primarily in the North Central States and New York and affects mainly children in rural or suburban areas.

Except in epidemics, the clinical findings in meningitis and encephalitis rarely permit specific identification. Headache, drowsiness, fever, vomiting, and stiff neck are the usual presenting symptoms. Tremors, mental confusion, convulsions, and coma may develop rapidly. Paralysis of the extremities occurs occasionally.

YELLOW FEVER

An acute Flavivirus *infection of variable severity, characterized by sudden onset, fever, a relatively slow pulse, and headache.*

Etiology and Epidemiology

Yellow fever occurs in two forms. In **urban yellow fever,** the virus is transmitted by the bite of an *Aedes aegypti* mosquito infected 2 wk previously by feeding on a viremic patient. In **jungle (sylvatic) yellow fever,** the virus is transmitted by *Haemagogus* and other forest canopy mosquitoes that acquire the virus from wild primates. Yellow fever is endemic in Central Africa and areas of South and Central America.

Symptoms and Signs

Cases are classified as inapparent (≤ 48 h of fever and headache), mild, moderately severe, and malignant. Incubation lasts 3 to 6 days. Prodromal symptoms are usually absent. Onset is sudden, with fever of 39 to 40° C (102 to 104° F). The pulse, usually rapid

TABLE 162–6. ARBOVIRUS AND ARENAVIRUS DISEASES

Major Clinical Syndrome	Viral Agent/Disease	Genus	Vector	Major Distribution
Fever, malaise, headaches, myalgia	Colorado tick fever	Orbivirus	Tick	Western USA, western Canada
	Phlebotomus fever	Phlebovirus	Sandfly	Mediterranean basin, Balkans, Middle East, Pakistan, India, China, eastern Africa, Panama, Brazil
	Venezuelan equine encephalitis	Alphavirus	Mosquito	Argentina, Brazil, northern South America, Panama, Mexico, Florida
	Rift Valley fever	Phlebovirus	Mosquito	South Africa, eastern Africa, Egypt
Fever, malaise, headaches, myalgia, lymphadenopathy, rash	Dengue fever	Flavivirus	Mosquito	Southeast Asia, Africa, Oceania, Australia, South America, Mexico, Caribbean
	West Nile fever	Flavivirus	Mosquito	Africa, Middle East, southern France, former Soviet Union, India, Indonesia
Fever, malaise, headaches, myalgia, arthralgia, rash	Chikungunya	Alphavirus	Mosquito	Africa, India, Guam, Southeast Asia, New Guinea
	Mayaro virus	Alphavirus	Mosquito	Brazil, Bolivia
	Ross River virus	Alphavirus	Mosquito	Australia, New Guinea, Solomon Islands, Samoa, Cook Islands
	Barmah Forest virus	Alphavirus	Mosquito	Australia
	Sindbis virus disease (Okelbo disease, Karelian fever)	Alphavirus	Mosquito	Africa, Australia, former Soviet Union, Finland, Sweden
Fever with CNS involvement	Eastern equine encephalitis	Alphavirus	Mosquito	Atlantic and Gulf coasts of USA, Caribbean, upper New York, western Michigan
	Western equine encephalitis	Alphavirus	Mosquito	USA, Canada, Central and South America
	St. Louis encephalitis	Flavivirus	Mosquito	USA, Caribbean
	Venezuelan equine encephalitis	Alphavirus	Mosquito	Argentina, Brazil, northern South America, Panama, Mexico, Florida
	Japanese encephalitis	Flavivirus	Mosquito	Japan, Korea, China, India, Philippines, Southeast Asia, former Soviet Union (eastern)

Major Clinical Syndrome
Fever with CNS involvement (*continued*)
Fever, malaise, headaches, myalgia, hemorrhagic signs
Fever, malaise, headaches, myalgia, respir tory failure

Modified from S edited by KJ Isselb

nus	Vector	Major Distribution
irus	Tick	Western USA, western Canada
ovirus	Sandfly	Mediterranean basin, Balkans, Middle East, Pakistan, India, China, eastern Africa, Panama, Brazil
virus	Mosquito	Argentina, Brazil, northern South America, Panama, Mexico, Florida
ovirus	Mosquito	South Africa, eastern Africa, Egypt
irus	Mosquito	Southeast Asia, Africa, Oceania, Australia, South America, Mexico, Caribbean
irus	Mosquito	Africa, Middle East, southern France, former Soviet Union, India, Indonesia
virus	Mosquito	Africa, India, Guam, Southeast Asia, New Guinea
virus	Mosquito	Brazil, Bolivia
virus	Mosquito	Australia, New Guinea, Solomon Islands, Samoa, Cook Islands
virus	Mosquito	Australia
virus	Mosquito	Africa, Australia, former Soviet Union, Finland, Sweden
virus	Mosquito	Atlantic and Gulf coasts of USA, Caribbean, upper New York, western Michigan
irus	Mosquito	USA, Canada, Central and South America
rus	Mosquito	USA, Caribbean
irus	Mosquito	Argentina, Brazil, northern South America, Panama, Mexico, Florida
rus	Mosquito	Japan, Korea, China, India, Philippines, Southeast Asia, former Soviet Union (eastern)

TABLE 162–6. ***Continued***

Major Clinical Syndrome	Viral Agent/Disease	Genus	Vector	Major Distribution
Fever with CNS involvement (*continued*)	California group virus	Bunyavirus	Mosquito	North Central States, New York
	Powassan virus	Flavivirus	Tick	Eastern Canada, New York
	Murray Valley encephalitis	Flavivirus	Mosquito	Australia, New Guinea
	Kyasanur Forest disease	Flavivirus	Tick	India
	Tick-borne encephalitis virus	Flavivirus	Tick	Europe, Balkans, former Soviet Union
	Lymphocytic choriomeningitis	Arenavirus	Rodent	USA, Argentina, Germany, Balkans
Fever, malaise, headaches, myalgia, hemorrhagic signs	Yellow fever	Flavivirus	Mosquito	Central and South America, Africa
	Dengue hemorrhagic fever	Flavivirus	Mosquito	Southeast Asia, Oceania, Caribbean
	Kyasanur Forest disease	Flavivirus	Mosquito	India
	Omsk hemorrhagic fever	Flavivirus	Tick	Former Soviet Union
	Crimean-Congo hemorrhagic fever	Nairovirus	Tick	Africa, eastern Europe, Middle East, former Soviet Union
	Hantaan virus	Hantavirus	Rodent	Korea, Japan, China, Southeast Asia, Europe
	Seoul virus	Hantavirus	Rodent	Korea, Japan
	Puumala virus	Hantavirus	Rodent	Scandinavia, former Soviet Union
	Machupo virus	Arenavirus	Rodent	Bolivia
	Junin virus	Arenavirus	Rodent	Argentina
	Guanaritovirus	Arenavirus	Rodent	Venezuela
	Lassa fever	Arenavirus	Rodent, human to human	West Africa
	Marburg virus	Filovirus	Unknown, human to human	Zimbabwe, Kenya, Uganda
	Ebola virus	Filovirus	Unknown, human to human	Zaire, Sudan
Fever, malaise, headaches, myalgia, respiratory failure	Hantavirus: Sin Nombre, Black Creek Canal, Bayou, New York-1, Rio Mamore	Hantavirus	Rodent	USA (west of Mississippi River), Canada, Brazil, Bolivia, Paraguay, Argentina

Modified from Sanford JP: "Arbovirus infections," in *Harrison's Principles of Internal Medicine*, ed. 13, edited by KJ Isselbacher, E Braunwald, JD Wilson, et al. New York, McGraw-Hill, Inc., 1994, p. 837.

initially, by the 2nd day becomes slow for the degree of fever present (Faget's sign). The face is flushed and the eyes are injected; the tongue margins are red and the center is furred. Nausea, vomiting, constipation, headache, muscle pains (especially in the neck, back, and legs), severe prostration, restlessness, and irritability are common symptoms. In mild cases, the illness ends at this stage after 1 to 3 days. In moderately severe and malignant cases, the fever falls suddenly 2 to 5 days after onset, and a remission of several hours or days ensues. The fever recurs but the pulse remains slow. Jaundice, extreme albuminuria, and epigastric tenderness with hematemesis, the characteristic triad, appear. Oliguria or anuria may occur; petechiae and mucosal hemorrhages are common. The patient is dull, confused, and apathetic. In malignant cases, delirium, convulsions, and coma occur terminally. Moderately severe cases may last 3 days to > 1 wk; the period of convalescence is usually short, except in the most severe cases. There are no known sequelae.

Diagnosis

Albuminuria occurs in 90% of patients, usually on the 3rd day, and may reach 20 g/L in severe cases. The WBC count, usually low, drops to 1500 to 2500/μL by the 5th day; leukocytosis may occur terminally. The pathogenesis of the bleeding is multiple: decreased synthesis of vitamin K-dependent coagulation factors secondary to the liver disease, disseminated intravascular coagulation, and altered platelet function. Thrombocytopenia and prolonged clotting and prothrombin times are common. In less acute cases, some of these laboratory findings may not occur. Serum bilirubin levels are mildly elevated.

Diagnosis is confirmed by isolation of the virus from the blood, by a rising antibody titer, or at autopsy by the characteristic midzonal liver cell necrosis. Needle biopsy of the liver during illness is contraindicated by the risk of hemorrhage.

Prognosis and Prophylaxis

Up to 10% of patients with clinically diagnosed cases die, but overall mortality is actually lower, since many mild or inapparent infections are undiagnosed.

Active immunization with the 17D strain of live, attenuated yellow fever vaccine (0.5 mL sc q 10 yr) effectively prevents outbreaks and sporadic cases. In the USA, the vaccine is given only at U.S. Public Health Service-authorized Yellow Fever Vaccination Centers. Vaccination requirements vary by country; current information and addresses of vaccination centers can be obtained from state and local health departments.

To prevent further mosquito transmission, patients should be isolated in well-screened rooms sprayed with residual insecticides. Since infection can be transmitted through laboratory accidents, hospital and laboratory personnel should be careful to avoid inoculating themselves with patients' blood.

Eradication of urban yellow fever requires widespread mosquito control and mass immunization. During sylvatic outbreaks, work in the area should be discontinued pending immunization and mosquito control.

Treatment

Supportive treatment is directed toward alleviating major symptoms. Complete bed rest and nursing care are important. Correction of fluid and electrolyte imbalance is imperative (see Ch. 12).

Hemorrhagic tendencies should be treated with calcium gluconate 1 g IV daily or bid or with phytonadione (see VITAMIN K DEFICIENCY in Ch. 3). Transfusion may be necessary. Heparin therapy should be considered if disseminated intravascular coagulation is evident (see under ACQUIRED COAGULATION DISORDERS in Ch. 131).

Nausea and vomiting may be alleviated with dimenhydrinate 50 to 100 mg po or 50 mg IM q 4 to 6 h or with prochlorperazine 5 to 10 mg po, parenterally, or rectally q 4 to 6 h. Fever may be reduced with tepid-water sponge baths. Aspirin is contraindicated because of its antiplatelet activity.

DENGUE

(Breakbone or Dandy Fever)

An acute febrile disease of sudden onset with headache, fever, prostration, severe joint and muscle pain, lymphadenopathy, and a rash that appears with a second temperature rise after an afebrile period.

Epidemiology

Dengue is endemic throughout the tropics and subtropics; outbreaks have occurred since 1969 in the Caribbean, including

Puerto Rico and the U
Cases have also been in
returning from Tahiti. Th
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Dengue hemorrhagi
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by acute onset followe
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called Philippine, Thai,
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Symptoms and Signs

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163 / HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Infection caused by one of two related retroviruses (HIV-1 and HIV-2) resulting in a wide range of clinical manifestations varying from asymptomatic carrier states to severely debilitating and fatal disorders related to defective cell-mediated immunity.

Some retroviruses are oncogenic, and others have pathologic effects that alter normal cell function or produce cell death. Of the retroviruses known to infect humans, human T-cell lymphotrophic virus (HTLV) types I and II are associated with lymphoid neoplasms and neurologic disease and less commonly with severe immunosuppression, whereas HIV causes immunosuppression but does not appear to cause neoplasms directly.

HTLV-I and HTLV-II are both lymphotropic and oncogenic, type C retroviruses, causing adult T-cell leukemia/lymphomas in < 5% of infected persons. Expansion of $CD4^+$ T (helper) lymphocytes in the tissues and circulation leads to leukemia, diffuse lymphadenopathy, hepatosplenomegaly, and skin lesions. Many patients appear to be immunosuppressed and some are subject to the same opportunistic infections as those with advanced HIV infections. HTLV-I is also neurotropic, causing a progressive myelopathy (tropical spastic paraparesis or HTLV-associated myelopathy [HAM]) in < 1% of carriers. A few cases of myelopathy have been described in HTLV-II carriers. Clinically, HAM is a progressive spastic paraparesis with weakness, stiffness, numbness, dysesthesias of the legs, and urinary frequency and incontinence presenting within the first decade after infection. (See also TROPICAL SPASTIC PARAPARESIS/HTLV-I–ASSOCIATED MYELOPATHY in Ch. 162.)

HTLV-I is transmitted sexually and through blood, but most infections appear to be transmitted vertically from mother to child by breastfeeding. The patterns of disease and seroprevalence for HTLV-I suggest that it is widely, but not homogeneously, distributed. For example, high levels of HTLV-I are present in southern Japan and the Caribbean and among IV drug users and prostitutes in some U.S. cities.

The human retrovirus that has had the greatest social and medical impact is HIV-1, which was identified in 1984 as the cause of a widespread epidemic of severe immunosuppression called **acquired immunodeficiency syndrome (AIDS).**

AIDS is a disorder of cell-mediated immunity characterized by opportunistic infections, malignancies, neurologic dysfunction, and a variety of other syndromes. AIDS is the most severe manifestation of a spectrum of HIV-related conditions (see Symptoms and Signs, below). The risk that an untreated person infected with HIV will develop AIDS is estimated to be 1 to 2%/yr in the first several years after infection and about 5%/yr thereafter. The cumulative risk is about 50% in the first decade. Almost all untreated HIV-infected persons will eventually develop AIDS. Some long-term sequelae of HIV infection (eg, other malignancies and chronic neurologic diseases) may not yet have been elucidated.

AIDS was initially defined by the development of serious opportunistic infections and/or certain secondary cancers, such as Kaposi's sarcoma and non-Hodgkin's lymphoma, known to be associated with defective cell-mediated immunity. The Centers for Disease Control and Prevention's 1993 definition categorizes adolescents and adults as asymptomatic (A), symptomatic with conditions attributable to HIV (B), and true AIDS (C); see TABLES 163–1 and 163–2. HIV patients are also categorized by $CD4^+$ lymphocyte counts: > 500 cells/μL (1), 200 to 499 cells/μL (2), < 200 cells/μL (3). Many patients first become aware of their HIV infection when diagnosed with a life-threatening opportunistic infection or malignancy without having experienced preceding chronic symptoms.

Transmission

HIV transmission requires contact with body fluids containing infected cells or plasma. HIV may be present in any fluid or exudate that contains plasma or lympho-

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ısmission

V transmission requires contact with fluids containing infected cells or na. HIV may be present in any fluid or ate that contains plasma or lympho-

TABLE 163–1. CONDITIONS ATTRIBUTABLE TO HIV OR COMPLICATED BY HIV (CATEGORY B)

Bacillary angiomatosis
Candidiasis, oropharyngeal (thrush)
Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
Constitutional symptoms, such as fever (38.5° C) or diarrhea lasting > 1 mo
Hairy leukoplakia, oral
Herpes zoster (shingles), involving at least 2 distinct episodes or more than one dermatome
Idiopathic thrombocytopenic purpura
Listeriosis
Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
Peripheral neuropathy

cytes, specifically blood, semen, vaginal secretions, breast milk, saliva, or wound exudates. Although theoretically possible, transmission by saliva or droplet nuclei produced by coughing or sneezing is extremely rare, if it occurs. HIV is *not* transmitted by casual contact or even by the close nonsexual contact that occurs at work, school, or home. The most common means of transmission is direct transfer of bodily fluids either through sharing contaminated needles or sexual relations.

Sexual practices involving no exposure to bodily fluids are safe. Other practices, such as fellatio and cunnilingus appear to be relatively, but not absolutely, safe. The greatest risk is through genital intercourse, especially anal-receptive intercourse. Sexual practices producing mucosal trauma before or during intercourse increase the risk. Use of latex, but not natural membrane, condoms or vaginal barriers decreases but does not eliminate risk. Oil-based lubricants decrease the protection provided by latex condoms because they dissolve them.

Infected cells or free virions can reach target cells in a new host via blood transfusion, accidental injection, or mucous membrane exposure. The role of mucous membrane inflammation is illustrated by the effect of other sexually transmitted diseases (STDs) on susceptibility to HIV infection. HIV transmission is definitely increased by chancroid and may be more likely in the presence of herpes, syphilis, trichomoniasis, and possibly other STDs.

Transmission of HIV by **needle-stick** injury, estimated at about 1/300 incidents, is much less frequent than transmission of hepatitis B, presumably because of the relatively lower number of HIV virions in the blood of most infected patients. Risk of HIV transmis-

TABLE 163–2. AIDS-INDICATOR CONDITIONS (CATEGORY C)

Candidiasis of bronchi, trachea, or lungs
Candidiasis, esophageal
Cervical cancer, invasive*
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (> 1 mo duration)
Cytomegalovirus disease (other than liver, spleen, or nodes)
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV-related
Herpes simplex: chronic ulcer(s) (> 1 mo duration); or bronchitis, pneumonitis, or esophagitis
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (> 1 mo duration)
Kaposi's sarcoma
Lymphoma, Burkitt's (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *M. kansasii*, disseminated or extrapulmonary
M. tuberculosis, any site (pulmonary* or extrapulmonary)
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis carinii pneumonia
Pneumonia, recurrent*
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain
Wasting syndrome due to HIV

*Added in the 1993 expansion of the AIDS surveillance case definition.

sion appears to be increased by deep wounds or injection of blood, such as when hollow-bore needles containing blood penetrate the skin.

Risk of HIV transmission **from infected medical personnel** who observe good techniques to uninfected patients is very small but is less clear. Transmission from a single dentist to at least six of his patients has been documented. However, extensive investigations of patients cared for by other HIV-infected physicians and surgeons have failed to uncover other cases. The means of transmission of HIV from the dentist to his patients is not understood and remains a troubling, but apparently unique, episode. Procedures or situations from which HIV-infected medical personnel should be excluded have not been clearly identified. Transmission of HIV during medical care is a potential problem if transfused blood is not screened or medical instruments are not adequately sterilized.

Use of enzyme-linked immunosorbent assay (ELISA) (see below) **to screen blood donors** has vastly reduced the risk of acquiring HIV by transfusion. However, persons in the early stages of HIV infection, who have not yet mounted an antibody response, may have transiently negative ELISA and Western blot results while yielding positive results for HIV p24 antigen in plasma. These persons may account for the very low, but continuing, risk of transfusion-associated HIV infection (estimated at between 1/10,000 and 1/100,000 per unit transfused). Currently mandated screening for both antibody and p24 antigen may further reduce this risk.

Pathogenesis

Two closely related retroviruses, HIV-1 and HIV-2, have been identified as causing AIDS in different geographic regions. HIV-1 causes most cases of AIDS in the Western Hemisphere, Europe, Asia, and Central, South, and East Africa; HIV-2 is the principal agent of AIDS in West Africa and appears less virulent than HIV-1. In certain areas of West Africa, both organisms are prevalent.

All retroviruses contain an enzyme called reverse transcriptase that converts viral RNA into a proviral DNA copy that becomes integrated into the host cell DNA. These integrated proviruses are duplicated by normal cellular genes each time the cell divides. Thus, all progeny of the originally infected cell will contain the retroviral DNA. The proviral HIV DNA is both transcribed to RNA and translated to proteins to produce hundreds of copies of the infectious virus. Critical to the final step in the life cycle of HIV is another enzyme, HIV protease. This enzyme converts immature, noninfectious HIV to its infectious form by splitting crucial proteins so they can rearrange within the virus after it has budded from an infected human cell.

HIV infects a major subset of T lymphocytes defined phenotypically by the T4 or CD4 transmembrane glycoprotein and functionally as helper/inducer cells. HIV also infects nonlymphoid cells, such as macrophages, microglial cells, and various endothelial and epithelial cells. Dendritic cells in the lymph nodes can bind HIV at the cell surface but are not invaded. As a result of HIV infection, the numbers and functions of T cells, B cells, natural killer cells, and monocytes-macrophages are disturbed. Despite abnormalities of cells other than $CD4^+$ lymphocytes, much of the immunologic dysfunction in AIDS appears to be explained by loss of the helper function of these lymphocytes, which is critical to cell-mediated immunity (see Ch. 146).

The best **predictors of onset** of the serious opportunistic infections that define AIDS (see TABLE 163–1) are the total number of circulating $CD4^+$ lymphocytes (CD4 count) and the level of HIV RNA in plasma (viral load). **The CD4 count** is the product of the WBC count, the percentage of lymphocytes in the WBCs, and the percentage of lymphocytes that bear the CD4 marker. Normal counts are about 750 ± 250 cells/μL, but levels are usually reduced by about 40 to 50% early in HIV infection. Vulnerability to opportunistic infections increases markedly when CD4 lymphocyte levels are < 200/μL. Other evidence of decreased cell-mediated immunity is loss of delayed hypersensitivity to intradermally injected antigens such as the PPD skin test for TB. The **viral load** (number of HIV-1 RNA copies in 1 mL of plasma) provides a useful predictor of future clinical course and measure of responses to antiretroviral therapy. Levels of HIV-1 RNA increase with advancing immunosuppression, but high levels also predict the future rates of decline in CD4 counts, even in patients without symptoms or evidence of severe immunosuppression (> 500 CD4 cells/

all progeny of the originally infected ill contain the retroviral DNA. The pro- HIV DNA is both transcribed to RNA anslated to proteins to produce hun- of copies of the infectious virus. Crit- the final step in the life cycle of HIV is er enzyme, HIV protease. This enzyme rts immature, noninfectious HIV to its ous form by splitting crucial proteins can rearrange within the virus after udded from an infected human cell. infects a major subset of T lympho- lefined phenotypically by the T4 or nsmembrane glycoprotein and func- as helper/inducer cells. HIV also in- onlymphoid cells, such as macro- microglial cells, and various lial and epithelial cells. Dendritic the lymph nodes can bind HIV at the face but are not invaded. As a result nfection, the numbers and functions ls, B cells, natural killer cells, and tes-macrophages are disturbed. De- normalities of cells other than $CD4^+$ ytes, much of the immunologic dys- in AIDS appears to be explained by ie helper function of these lympho- hich is critical to cell-mediated im- see Ch. 146).

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Suppressor/cytotoxic $CD8^+$ lymphocytes appear to be functionally normal and increased in number in HIV infection, which may contribute further to immunosuppression and results in reduction of the **CD4:CD8 ratio** (normally ≈ 2:1) to < 1. Because other viral infections (eg, CMV, Epstein-Barr virus, influenza, hepatitis B) may produce transient reductions in the CD4:CD8 ratio, decreased ratios are not specific.

Concepts of how HIV disrupts the immune system have been radically changed by the discovery of high rates of both production and removal of HIV, as revealed by the rapid reduction of plasma HIV RNA during treatment with potent antiretroviral drugs. The median turnover time of HIV RNA in plasma (time taken for half of HIV virions to be replaced) is estimated to be less than a day, corresponding in moderate to heavy HIV infection to a turnover of about 10^8 to 10^9 virions/day. This rapid viral replication provides many opportunities for mutation and thereby the possibility for rapid emergence of viral mutants resistant to antiretroviral drugs. For infected CD4 cells, the half-life is slower (about 2 days). It appears that newly infected CD4 cells contribute > 99% of plasma RNA; after about 2 days of viral replication, these cells die. Thus, even asymptomatic patients are constantly destroying their CD4 cells at rates determined by the level of plasma RNA. During effective drug therapy, plasma HIV RNA levels fall within days and reach lower plateaus or become undetectable within a few weeks or months. These insights and a host of powerful new antiretroviral drugs have radically changed the approach to antiretroviral therapy (see below).

The relationship of RNA in plasma to levels in lymph nodes and the brain is under intense investigation because the effect of treatment on these reservoirs of HIV in the body is unclear. Even when combination therapy reduces plasma HIV RNA to unmeasurable levels, virus remains detectable in lymph nodes for several years. CSF levels of HIV RNA in patients treated effectively with drugs such as nucleoside analog reverse transcriptase inhibitors (eg, zidovudine or stavudine) are usually unmeasurable and may reflect levels in the brain, but this is not yet proven. Targeting HIV in these reservoirs may be a crucial step in eliminating HIV infection in individual patients.

The **pattern of loss of $CD4^+$ lymphocytes** proceeds in three phases and at rates that vary from patient to patient. Within the first months of infection, circulating $CD4^+$ cell numbers drop rapidly. A prolonged period of slower decline may be followed by another more rapid decline in the 1- to 2-yr period before AIDS develops. Variation in lymphocyte depletion rates over time and between persons appears to correlate with levels of HIV RNA in plasma. The mechanisms underlying cell destruction are not fully understood, however.

Humoral immunity is also affected. Hyperplasia of B (antibody-producing) lymphocytes in lymph nodes causes lymphadenopathy and increased secretion of antibodies, leading to hyperglobulinemia. Production of antibodies to previously encountered antigens persists; however, response to new antigens is defective and sometimes absent. Thus, total antibody levels (especially IgG and IgA) may be elevated and titers of antibodies to specific agents (eg, cytomegalovirus) unusually high, but response to immunizations increasingly declines as CD4 counts decline.

The measurable **immunologic abnormalities** in AIDS include anergy (demonstrated by lack of delayed hypersensitivity responses to intradermal injection of common antigens; eg, tetanus, mumps, *Candida albicans*), poor T-cell proliferative responses to mitogens and antigens, polyclonal hypergammaglobulinemia, elevated plasma immune complex levels, diminished antibody responses to both recall and new antigens, decreased natural killer function, and increased levels of markers of immune activation such as α_1-thymosin, acid-labile interferon, neopterin, and β_2-microglobulin.

Opportunistic infections: Patterns of specific opportunistic infections vary geographically, among risk groups, and as a result of medical interventions. In the USA and Europe, > 90% of AIDS patients with Kaposi's sarcoma are homosexual or bisexual men, probably because they are co-infected with human herpesvirus 8, a newly identified viral cofactor (with HIV) for Kaposi's sarcoma. Toxoplasmosis and TB are more common in tropical areas where the prevalence

of latent infections with *Toxoplasma gondii* and *Mycobacterium tuberculosis* in the general population is high. Even in developed countries where background levels of TB are low, HIV has caused increased rates and atypical presentations of TB. Widespread use of effective prophylaxis against such agents as *Pneumocystis carinii* and *Mycobacterium avium* complex has reduced the risk of these infections in developed countries.

Epidemiology

Since AIDS was first recognized in 1981 when cases of *Pneumocystis carinii* pneumonia and Kaposi's sarcoma were reported in homosexual men in California and New York, > 581,000 cases and 357,000 deaths have been reported through December 1996 in the USA. Over 30 million HIV infections and 10 million AIDS cases are estimated worldwide.

Two epidemiologic patterns of HIV transmission are recognized. In the **USA and Europe (type 1)**, transmission is primarily homosexual or via blood. Most patients are 20- to 49-yr-old men in high-risk groups (eg, homosexual or bisexual men, IV drug users who share needles, and recipients of transfused blood or blood components who sometimes transmit HIV to women heterosexually). In the USA, women are an increasing proportion (about 20%) of all AIDS cases.

Among persons with hemophilia and other bleeding disorders, AIDS has become the leading cause of death. Before 1985, the risk of HIV infection among hemophiliacs correlated with large requirements for factor VIII concentrates and the origin of their plasma products in the USA. The wide distribution of commercial plasma products originating in the USA resulted in a high rate of HIV infection, even in recipients from areas not initially affected by the epidemic. In most of Europe, where clotting factor material was collected from populations with lower risk of HIV infection, fewer hemophiliacs were infected. However, routine use of screened and heat-treated blood or bioengineered treatments for hemophilia has subsequently eliminated the risk of infection.

In **Africa, South America, and Southern Asia (type 2)**, transmission is primarily heterosexual. In these areas, men and women are nearly equally affected. Mixtures of the two patterns have been found in countries such as Brazil and Thailand. Typically, diseases follow routes of transportation and trade to cities and secondarily to rural areas.

The continuing spread of HIV in developing countries with minimal resources with which to manage the epidemic has grave implications. The spread of two distinct serogroups of HIV-1 in Thailand is illustrative. In about 1990, parallel epidemics of heterosexually transmitted (genotype A) and needle-transmitted (genotype B) HIV rapidly infected female prostitutes and their clients and IV opiate users who shared needles.

Infection of large numbers of women of childbearing age has led to a substantial number of **pediatric cases of AIDS**. (see HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN CHILDREN under VIRAL INFECTIONS in Ch. 265). HIV can be transmitted transplacentally or perinatally. The virus has been found in breast milk, and breastfeeding has been implicated in transmission. In addition, groups of newborns and children have become infected from repeated use of inadequately sterilized needles.

Symptoms and Signs

HIV causes a broad spectrum of clinical problems, which may mimic other diseases. Immediately after infection and for a prolonged period (more than several months in a small number of persons), there is a brief antibody-negative carrier state. During this time, the virus reproduces rapidly until the immune system begins to react and/or targets are exhausted. HIV RNA or HIV p24 (capsid) antigen is detectable in plasma, even when no antibody to HIV is detectable. Within 1 to 4 wk after infection, some patients develop **acute retroviral syndrome** or **primary HIV infection** with fever, malaise, rash, arthralgias, and generalized lymphadenopathy, usually lasting 3 to 14 days, followed within days to 3 mo by seroconversion for antibody to HIV. Acute retroviral syndrome is frequently misdiagnosed as a febrile upper respiratory illness ("flu") or mononucleosis. Subsequently, these acute manifestations disappear (although lymphadenopathy usually persists) and patients become **antibody-positive, asymptomatic HIV carriers.** Some of these patients develop mild, remittent symptoms and signs that do not meet the definition of AIDS (eg, thrush, zoster, diarrhea, fatigue, fevers). Leukopenia is common and anemia and im-

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Infection of large numbers of women of childbearing age has led to a substantial number of **pediatric cases of AIDS** (see HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN CHILDREN under VIRAL INFECTIONS in Ch. 265). HIV can be transmitted transplacentally or perinatally. The virus has been found in breast milk, and breastfeeding has been implicated in transmission. In addition, groups of newborns and children have become infected from repeated use of inadequately sterilized needles.

Symptoms and Signs

HIV causes a broad spectrum of clinical problems, which may mimic other diseases. Immediately after infection and for a prolonged period (more than several months in a small number of persons), there is a brief antibody-negative carrier state. During this time, the virus reproduces rapidly until the immune system begins to react and/or targets are exhausted. HIV RNA or HIV p24 (capsid) antigen is detectable in plasma, even when no antibody to HIV is detectable. Within 1 to 4 wk after infection, some patients develop **acute retroviral syndrome** or **primary HIV infection** with fever, malaise, rash, arthralgias, and generalized lymphadenopathy, usually lasting 3 to 14 days, followed within days to 3 mo by seroconversion for antibody to HIV. Acute retroviral syndrome is frequently misdiagnosed as a febrile upper respiratory illness ("flu") or mononucleosis. Subsequently, these acute manifestations disappear (although lymphadenopathy usually persists) and patients become **antibody-positive, asymptomatic HIV carriers.** Some of these patients develop mild, remittent symptoms and signs that do not meet the definition of AIDS (eg, thrush, zoster, diarrhea, fatigue, fevers). Leukopenia is common and anemia and immune-mediated thrombocytopenia may also occur.

Neurologic symptoms: Neurologic symptoms are common and may be the first manifestation of AIDS. Symptoms may be due to direct effects of HIV, opportunistic infections, neoplasms, or vascular complications. They include acute aseptic meningitis; peripheral neuropathies of several types; encephalopathy with seizures; focal motor, sensory, or gait deficits; and cognitive dysfunction progressing to dementia (see NON-ALZHEIMER'S DEMENTIAS in Ch. 171).

Peripheral neuropathy may cause painful dysesthesias, moderate distal sensory loss (stocking-glove distribution), depressed ankle reflexes, distal weakness, and atrophy and can occur in varying degrees. Either Guillain-Barré syndrome or cytomegalovirus (CMV) polyradiculopathy may present as ascending paralysis.

Myopathy similar to polymyositis may complicate AIDS or zidovudine therapy.

Aseptic meningitis may cause headache, fever, and photophobia and may be associated with a CSF mononuclear pleocytosis. Transient aseptic meningitis may accompany primary HIV infection.

Subacute encephalitis may be caused by HIV, CMV, or both. Neuropathology at autopsy may reveal nodular collections of microglial cells without other inflammatory infiltrates in gray matter. Intranuclear and intracytoplasmic inclusions of CMV are associated with the nodules in cases of CMV encephalitis. Small, poorly defined foci of perivenular demyelination are found in white matter. Headache, confusion, memory loss, psychomotor retardation, myoclonus, seizures, and severe dementia progressing to coma are typical findings spanning weeks to months before death. Cortical atrophy on CT, CSF pleocytosis and elevated protein level, and a diffusely abnormal EEG may be present but are nonspecific. Demonstration of CMV DNA to CSF by the polymerase chain reaction may be diagnostic of CMV encephalitis, ventriculitis, or myelitis/polyradiculopathy.

Less dramatic cognitive and motor disorders occur in many AIDS patients that are less clinically evident and socially debilitating and thus are not widely recognized. The areas of cognitive functioning more frequently affected are attention, speed of information processing, and learning. These cognitive abnormalities are not explained by mood disturbances or drug or alcohol abuse. They are associated with brain atrophy on MRI, immune activation (elevated β_2-microglobulin levels), measurable HIV RNA levels (> 200 copies/mL) in CSF, and other neurologic abnormalities. Mild cognitive and motor disorders do not necessarily progress rapidly to dementia, but many patients have slowly progressive deterioration. Response to treatment for either CMV or HIV encephalopathy has been documented but is not predictable.

CNS opportunistic infections: Toxoplasmic encephalitis causes headache, lethargy, confusion, seizures, and focal signs that evolve over days to weeks. CT or MRI findings include ring-enhancing lesions with a predilection for basal ganglia. Serologic tests for IgG antitoxoplasmal antibodies reflecting antecedent chronic latent infection are almost always positive but do not always prove that the lesion is caused by *Toxoplasma* organisms. Negative serologic tests greatly reduce the likelihood that a lesion is caused by *Toxoplasma gondii*. The CSF shows a mild to moderate pleocytosis and elevated protein content. Brain biopsy can be diagnostic; however, a therapeutic trial of pyrimethamine and sulfadiazine (or clindamycin if the patient is allergic to sulfadiazine) is often attempted with close observation for response in 7 to 10 days in seropositive patients. With treatment, the prognosis is good and recurrences can be prevented by lifelong prophylaxis with trimethoprim/sulfamethoxazole or clindamycin/pyrimethamine.

Cryptococcal, histoplasmal, and tuberculous *(Mycobacterium tuberculosis)* meningitides also present with fevers and headache in AIDS and are treatable. Progressive multifocal leukoencephalopathy (see Ch. 162), an encephalitis caused by papovaviruses, has not been responsive to therapy and is usually progressive and fatal within a few months.

Neoplasms of the brain: Primary B-cell CNS lymphoma (non-Hodgkin's) of the brain produces focal signs consistent with its anatomic location. CT usually shows a mass that is sometimes contrast-enhancing and cannot reliably be distinguished from focal encephalitis caused by *Toxoplasma*, TB, *Cryptococcus*, or other opportunistic organisms. In these cases, MRI may be more discriminating, and brain biopsy is necessary

for definitive diagnosis. Systemic lymphomas in AIDS may involve the CNS, but Kaposi's sarcoma rarely does. (See also Ch. 145.)

Hematologic symptoms: Some patients present with symptomatic anemia or immune-mediated thrombocytopenia. HIV-associated thrombocytopenia usually responds to the same interventions (corticosteroids, splenectomy, IV immune globulin) as idiopathic thrombocytopenic purpura and seldom leads to bleeding. (See also Ch. 145.)

GI symptoms: Abdominal pain, nausea and vomiting, or diarrhea contributes to the weight loss and wasting that so commonly afflicts advanced AIDS patients. Various opportunistic infections and tumors may involve the GI tract. Sites include the oropharynx (*Candida*, Kaposi's sarcoma, lymphoma, herpes simplex, and aphthous stomatitis), esophagus (herpes simplex, CMV, *Candida*), stomach (Kaposi's sarcoma and lymphoma), bowel (*Salmonella*, *Clostridium difficile*, CMV, herpes simplex virus), and biliary tract (cryptosporidium and CMV). In addition, drug-associated pancreatitis (eg, didanosine) or hepatitis (eg, fluconazole) may complicate therapy. Diarrhea for which no cause can be found may persist for long periods or recur intermittently, even in patients without severe immunosuppression or other symptoms.

Dermatologic symptoms: Skin manifestations of HIV infection complicate every stage from the rash and genital ulcers of primary infection to widespread Kaposi's sarcoma in AIDS (see Ch. 126). Zoster, which is common throughout the course of infection, is often the first manifestation. Hematogenous lesions of cryptococcosis or bacillary angiomatosis may be important clues to diagnosis of these opportunistic infections.

Oral symptoms: Oral candidiasis (thrush) is among the earliest and most common manifestations of HIV infection; it is usually painless, may not be noticed by the patient, and may provide a useful clue in undiagnosed patients. Oral hairy leukoplakia, diagnosed by finding asymptomatic enlarged, white, filiform patches on the sides of the tongue, is probably caused by Epstein-Barr virus and is treatable with acyclovir. Ulcers caused by herpes simplex or of unknown etiology (aphthous) may be large, painful, and persistent and may interfere with nutrition. Periodontal disease may become severe, leading to bleeding, swelling of gums, and loss of teeth. Both Kaposi's sarcoma and lymphomas may present in the oropharynx, usually as painless masses.

Pulmonary symptoms: By far the most important HIV-associated lung infection is TB, which is frequently the first manifestation of HIV infection where TB is heavily endemic. Atypical presentations (infrequent cavitation, lower-lobe infiltrates, miliary disease, and adenopathy), anergy to tuberculin skin tests, and confusion or coexistence with other opportunists may make the diagnosis difficult. The lung is also a common site for opportunistic infections caused by fungi such as *Pneumocystis carinii*, *Cryptococcus neoformans*, *Histoplasma neoformans*, *Coccidioides immitis*, and *Aspergillus* sp. Bacterial pneumonias caused by pneumococci, *Haemophilus*, *Pseudomonas*, and *Rhodococcus* are particularly common in IV drug users. Both Kaposi's sarcoma and B-cell lymphomas may involve mediastinal nodes and the lung.

Symptoms in women: The presentation and course of HIV infection in women resembles that in men overall with the exception of chronic refractory vaginal candidiasis and increased risk of cervical intraepithelial neoplasia. Some STDs such as pelvic inflammatory disease may be atypical, more aggressive, and resistant to treatment in HIV-infected women. HIV testing for women with recurrent, aggressive, or unusually resistant STDs or vaginal candidiasis is recommended.

Cardiovascular complications include marantic (thrombotic) or bacterial endocarditis (especially in IV drug abusers) or a cardiomyopathy with congestive heart failure.

Renal insufficiency or nephrotic syndrome uncommonly complicates AIDS, but may be a source of severe disability (see also Ch. 224).

Laboratory Diagnosis

The detection of antibodies to HIV is sensitive and specific at most stages of infection, inexpensive, and widely available. Rapid (10-min) serum tests, home collection systems, and tests for HIV antibody in oral secretions and urine are useful in some situations, but they require confirmation by standard serum testing. Detection of HIV RNA in blood provides a sensitive and specific diagnosis of HIV infection in patients in the very early

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Tests for detecting antibody to HIV include **ELISA**, which can detect antibodies to HIV proteins. ELISA is both highly sensitive and specific, but some false-positive ELISA tests occur. When reactive, ELISA *should be repeated on the same sample.* If it is positive a second time, a test that is more specific should be performed, eg, **the Western blot**, which is an immunoelectrophoretic procedure for identifying antibodies to specific viral proteins separated by their molecular weight.

ELISAs that directly measure viral antigens (p24) rather than antiviral antibodies are relatively insensitive. Tests of antigen levels have been supplanted by more sensitive measurements of plasma RNA.

Several sensitive **assays of plasma RNA**, such as the reverse-transcription polymerase chain reaction (RT-PCR), which amplifies viral nucleic acids, or the branched DNA (bDNA), which amplifies signal, are sensitive and accurate over a wide range of viral concentrations (up to 1,000,000 copies/mL of plasma). The lower limits of detection are about 400 copies/mL for RT-PCR and 5000 copies/mL for bDNA, and the sensitivity of these tests is being improved. Other methods for nucleic acid amplification, such as nucleic acid sequence-based amplification (NASBA) and transcription-mediated amplification (TMA), are under development to increase the sensitivity of HIV RNA quantitation.

Prognosis

An HIV-infected person's risk of developing AIDS or dying can be estimated by combining $CD4^+$ lymphocyte counts and levels of plasma RNA (see Pathogenesis, above). The $CD4^+$ count provides information on immediate vulnerability to opportunistic infections, and the plasma HIV RNA level predicts future $CD4^+$ levels. Reduction of plasma RNA levels by antiretroviral therapy reduces the risk of complications and death and often increases $CD4^+$ lymphocyte counts.

Opportunistic infections have remained the immediate cause of death for nearly all AIDS patients. Advances in prophylaxis have decreased the incidence of *Pneumocystis, Toxoplasma, Mycobacterium avium* complex (MAC), *Cryptococcus*, and other opportunistic infections, and consequently their contribution to morbidity and mortality. Better drug treatment of these infections and, to a lesser extent, of Kaposi's sarcoma has improved outcomes as well.

The introduction of combination antiretroviral drug therapy has dramatically prolonged the survival for patients with AIDS over periods of 2 to 3 yr, but the duration of benefit is variable and as yet incompletely defined. New antiretroviral drugs used in potent combinations and monitored by plasma viral (RNA) levels promise to extend the survival of patients at all stages of HIV infection. These benefits may be compromised by viral resistance as influenced by the patients' prior use and compliance with antiretrovirals and their stage of infection (see Treatment, below).

Prevention of HIV Transmission

Multiple strategies are being developed to induce protective immunity in persons not infected with HIV. **Immunogens** include attenuated live and whole killed HIV, genetically engineered HIV proteins and peptides (eg, from the viral envelope), and vaccinia virus genetically modified to express HIV viral proteins. These efforts are hampered by the lack of a measurable marker of protective immunity, such as the neutralizing antibody engendered by polio vaccine, or of a convenient animal model. Nevertheless, vaccines continue to be developed and tested for safety and immunogenicity.

Sexual contact with an HIV carrier remains the most common cause of transmission. **Education to avoid unsafe sexual practices** by reducing the number and frequency of sexual contacts, avoiding high-risk practices (eg, anal intercourse), and using barrier protection such as condoms is the cornerstone of prevention. Consistent use of condoms greatly reduces risk of transmission of HIV. The effect of antiretrovirals on transmission is uncertain, but will probably reduce the risk. Whether symptomatic or not or treated or not, HIV carriers should be regularly counseled to avoid unsafe sexual practices with uninfected persons.

All **pregnant women** should be offered a test for antibody to HIV. HIV-infected women should be advised to consider deferring pregnancy at least until management of HIV in pregnancy is better studied. The risk of transmission in utero, intrapartum, or postpartum transmission to the fetus is estimated to be

30 to 50%, but zidovudine (ZDV or AZT) alone reduces intrapartum infection by 2/3, and combinations of drugs may be more effective. Given the low, but real, risk of transmission even with treatment and the uncertainty of the effects on the fetus of drugs needed for their own health, termination of pregnancy may be an alternative for many HIV-infected pregnant women.

Parenteral drug users should be counseled about the risk of sharing needles. Ideally, this effort should be combined with rehabilitation and treatment of drug dependence.

Confidential testing for antibody to HIV should be offered to anyone requesting it, but only in conjunction with pretest and posttest counseling. Persons who are at high risk for contracting HIV infection—*even those with negative HIV antibody test results*—should not donate blood or organs for transplantation because of the small risk they may have been recently infected and be infectious but antibody-negative.

Isolation of hospitalized patients with HIV infection is unnecessary, except when their complicating infections (eg, suspected or proven TB) are communicable. Surfaces contaminated by blood or other body fluids should be cleaned and disinfected. HIV is readily inactivated by heat and many disinfectants, including peroxide, alcohols, phenolics, and hypochlorite. The body fluids and tissues of HIV-infected patients should be handled with extreme care.

Medical and dental professionals should wear gloves when examining *all* patients if contact with mucous membranes or other wet surfaces may occur. Because needle-stick accidents are common, health care workers must be taught how to avoid them.

Postexposure prophylaxis with immediate antiretroviral therapy after penetrating injuries involving HIV-infected blood (needle sticks) or heavy mucous membrane (eye or mouth) contamination is believed to reduce transmission. Combinations of a protease inhibitor with two nucleoside reverse transcriptase inhibitors are currently recommended for postexposure prophylaxis of relatively high-risk exposures. Zidovudine (ZDV or AZT) appeared to reduce risk of transmission after needle-stick injuries in one study, which provided the only evidence that prophylaxis works. Because of the low risk of infection for most injuries, controlled prospective studies of the effectiveness of prophylaxis are not practical. Cancers or birth defects from the brief exposures to these drugs have not been found in the small numbers of otherwise healthy persons who have used ZDV for this purpose. Because some women in early pregnancy will be offered postexposure prophylaxis before their pregnancy is suspected or confirmed, special caution must be exercised in treating potentially pregnant women. Additional problems arise when the source or HIV status of blood is unknown, but identification of the source and testing of that person for HIV infection should be vigorously pursued.

Prevention of Opportunistic Infections

Primary prophylaxis for ***P. carinii* pneumonia** should be recommended to patients with $CD4^+$ lymphocyte counts $< 200/\mu L$. The dosing interval necessary for maximum protection by the preferred drug, trimethoprim-sulfamethoxazole (TMP-SMX), has not been determined. Every-other-day dosing is better tolerated than daily double-strength dosing, and escalating regimens at the initiation of prophylaxis improves tolerance. Some patients who cannot tolerate TMP-SMX can tolerate dapsone. Because both the sulfonamides and sulfones provoke adverse effects (eg, fever, neutropenia, skin rashes), in a minority of patients, aerosolized pentamidine is a useful alternative.

Primary prophylaxis for **mycobacterial, toxoplasmal, and fungal infections** has been developed. Rifabutin, clarithromycin, and azithromycin can help prevent disseminated MAC infections in AIDS patients with CD4 counts < 50 cells/μL. Azithromycin may be preferred because it can be given weekly as two 600-mg tablets, provides protection (70%) similar to daily clarithromycin, and does not interact with other drugs. Preventing reactivation of TB is important for patients likely to have inactive infection with *Mycobacterium tuberculosis*. Daily treatment with isoniazid for 1 yr is recommended.

Risk of reactivation of ***Toxoplasma gondii***, especially in the brain, is indicated by antibodies (IgG) in serum that identify latent *Toxoplasma* infections. Toxoplasmal encephalitis is relatively uncommon in the USA because latent toxoplasmal infection is uncommon in the USA (about 15% of adults) compared with Europe and most developing countries and because TMP-SMX taken for

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prevention of pneumocystis pneumonia provides excellent protection.

For some **deep fungal infections** (eg, esophageal candidiasis or cryptococcal meningitis and pneumonia), primary prophylaxis with oral fluconazole taken daily (100 mg) or weekly (400 mg) has been successful. The cost of preventing these diseases is high and may not be indicated since they may be treated in most cases.

Secondary prophylaxis is indicated with fluconazole for patients with recurrent oral, vaginal, or esophageal candidiasis or for cryptococcal meningitis or pneumonia; and with itraconazole for histoplasmosis and possibly some forms of aspergillosis (see Ch. 158). Secondary prophylaxis is also indicated to prevent relapses of *P. carinii* pneumonia, cryptococcal infections, toxoplasmic encephalitis, and herpes simplex (see Chs. 73, 158, 161, and 154, respectively).

Treatment

Several new principles of treatment for HIV infection emerged in the mid-1990s. New methods to quickly measure the effects of drugs on HIV in the blood, ie, suppression of plasma HIV RNA levels, and a better understanding of the rapid production of HIV, even in the clinically inactive stages of infection, have changed the approach.

Combinations of drugs usually targeting two enzymes (HIV reverse transcriptase and protease) is now the standard, and use of single drugs is discouraged. Treatment with two to four drugs can promptly halt viral reproduction, preserve immune function, and decrease the likelihood of emergence of drug-resistant viral mutants. The length of response to various combinations of drugs varies with their success in completely suppressing viral replication, which usually requires consistent compliance with combinations of three potent drugs.

Plasma HIV RNA levels provide a means of rapidly and directly measuring effects of antiretroviral drugs. Therapeutic monitoring of RNA levels assesses the initial (at 4 to 8 wk) and ongoing (every 3 to 4 mo) effect of combination drug regimens. Reduction in plasma RNA has become the accepted method of measuring the effects of single or combinations of drugs. Increasing levels may indicate noncompliance with drugs or the emergence of genetic variants of HIV resistant to the drugs.

Treatment of patients with measurable plasma RNA levels (> 400 copies/mL) even when they have relatively high CD4 counts (> 500 cells/μL) is now recommended by some experts. Evidence to support this intensive and expensive approach to therapy in less advanced (CD4 > 500) patients remains circumstantial. The rapid rates of viral production and clearance demonstrated for most patients at all stages of HIV infection supports this approach.

Antiretroviral drugs: The antiretroviral drugs used to treat HIV infection are listed by their class in TABLE 163–3 by generic and abbreviated names. Their status of approval by the FDA in mid 1998 is also shown. Three of the four classes of available drugs act by inhibiting HIV reverse transcriptase; protease inhibitors interfere with activity of HIV protease (see Pathogenesis, above).

Most experts recommend that patients at any stage of HIV infection with more than 5000 HIV RNA copies/mL of plasma be treated with combination therapy, including two nucleosides (eg, ZDV and lamivudine [3TC]), two nucleosides and a protease inhibitor (eg, indinavir), or two nucleosides and a non-nucleoside reverse transcriptase inhibitor (eg, nevaripine). Although some drugs interact with others to influence their removal, in some cases this is helpful. For example, when two protease inhibitors, saquinavir and ritonavir, are combined, ritonavir helps to raise the levels of saquinavir by decreasing its removal.

Another useful interaction involves prevention of or compensation for selection of drug-resistant genetic mutants of HIV. For example, when given alone, 3TC quickly selects for HIV with a single mutation that allows HIV to grow in the presence of the drug. After a few months of ZDV alone, many patients develop a mutation that reduces the antiviral effect of ZDV. However, if 3TC and ZDV are given together, the combination achieves impressive suppression of HIV, even in patients with ZDV resistance, because the mutation for 3TC resistance increases the susceptibility of HIV to ZDV.

Combinations can be harmful if they increase or decrease elimination of one of the component drugs, leading to drug levels that are either too high or too low, or if they have combined toxicity. Information on drug combinations is rapidly accumulating and will inform future choices.

TABLE 163–3. ANTIRETROVIRAL DRUGS

Generic Name	Abbreviation	Usual Adult Dose (Oral)	Possible Adverse Effects*	FDA Status as of Mid 1998
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS				
Zidovudine	ZDV, AZT	300 mg bid	Anemia and leukopenia†, rarely pancreatitis	Approved
Didanosine	ddI	200 mg bid if > 60 kg; 125 mg bid if < 60 kg	Peripheral neuropathy,‡ pancreatitis§	Approved
Zalcitabine	ddC	0.75 mg tid	Peripheral neuropathy,‡ pancreatitis§	Approved
Stavudine	d4T	40 mg bid if > 60 kg; 30 mg bid if < 60 kg	Peripheral neuropathy,‡ rarely pancreatitis	Approved
Lamivudine	3TC	150 mg bid	Peripheral neuropathy,‡ rarely pancreatitis	Approved
Abacavir	—	300 mg bid	Severe hypersensitivity	Investigational
PROTEASE INHIBITORS‖				
Saquinavir	SAQ	600 mg tid	¶	Approved
Indinavir	IND	800 mg tid	Kidney stones, causing back pain, hematuria, or obstruction of the kidneys with decreased function	Approved
Ritonavir	RIT	600 mg bid	¶	Approved
Nelfinavir	NEL	750 mg tid	¶	Approved
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS				
Nevirapine	NVP	200 mg daily for 2 wk, then 200 mg bid	Rashes	Approved
Delavirdine	DLV	400 mg q 8 h	Rashes	Approved
Loviride	LVD	¶	¶	Investigational
Efavirenz	—	600 mg daily	CNS symptoms	Investigational
NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITOR				
Adefovir	bis-POM PMEA	125 mg daily	Fanconi's syndrome	Investigational

*Other adverse effects that may be caused by some or all drugs include headache, nausea, abdominal pain, diarrhea, loss of appetite, abnormal perioral sensation, loss or abnormality of taste.

†Can be treated with transfusions or other drugs such as erythropoietin for anemia or colony-stimulating factor (G-CSF or GM-CSF) for leukopenia.

‡Peripheral neuropathy may be reversible when the drug is stopped, and can be treated symptomatically with partial relief, if severe.

§Symptoms of pancreatitis, such as nausea and vomiting or back and abdominal pain, require that ddI or ddC be immediately discontinued until pancreatitis is confirmed or excluded.

‖Protease inhibitors may cause elevations in serum triglyceride levels of unknown clinical significance.

¶ Data insufficient or unavailable.

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The **adverse effects** of antiretroviral drugs, which vary by type of drug and dose, remain a central concern of both patients and physicians. Many adverse effects (eg, headache from ZDV) often become less severe over time, but others (eg, stomach pain from didanosine) may indicate serious problems (eg, pancreatitis) that require immediate action. Because some adverse effects (eg, anemia, pancreatitis, hepatitis, glucose intolerance) can be detected by blood tests before they cause symptoms, regular monitoring of hematology and serum chemistries as well as symptoms is crucial. Finally, duration of therapy is uncertain: drugs should be taken only for as long as the antiretroviral benefits outweigh adverse effects and costs. The serious adverse effects of antiretroviral drugs are listed in TABLE 163–3.

Drug resistance is more likely if patients are given inadequate numbers or doses of drugs or do not take drugs as instructed. Although drug combinations delay selection of resistant HIV mutants, they usually do not prevent it unless total suppression of viral replication is achieved. Close attention to patient compliance and plasma HIV RNA monitoring help limit the selection of resistant strains.

Some currently untreatable **CNS complications** of HIV (eg, progressive multifocal leukoencephalopathy) may respond to antiretroviral treatment if the primary immune defect is corrected. Responses to antiretroviral drugs have been documented for HIV-induced cognitive dysfunction. Measurement of levels of HIV RNA in CSF appears to provide a means of evaluating HIV replication and antiviral treatment effects to the brain, but the usefulness of CSF RNA monitoring has not yet been demonstrated.

End-of-life care: Even with combined therapy, AIDS remains a terminal disease. At some time, relief of pain and suffering may become the focus of treatment, and patients may opt for hospice care (see Ch. 294).

164 / SEXUALLY TRANSMITTED DISEASES

(See also Ch. 163.)

The incidence of sexually transmitted diseases (STDs), among the most common communicable diseases in the world, steadily increased from the 1950s to the 1970s but generally stabilized in the 1980s. The incidence of some diseases (eg, syphilis and gonorrhea) decreased from the mid-1980s to the mid-1990s in the USA and elsewhere. Nonspecific urethritis, trichomoniasis, chlamydial infections, genital and anorectal herpes and warts (all discussed in this chapter), scabies, pediculosis pubis, and molluscum contagiosum (see Chs. 114 and 115) are probably more prevalent than the five historically defined venereal diseases—syphilis, gonorrhea, chancroid, lymphogranuloma venereum, and granuloma inguinale. However, because the latter diseases are more consistently reported, reliable incidence rates for the others are not available.

In 1995, worldwide incidence of gonorrhea was estimated at > 250 million cases (USA, about 400,000); for syphilis, 50 million cases (USA, about 70,000, including about 16,000 primary and secondary cases and 1,500 congenital cases). Chlamydial STDs now approach 1/2 million reported cases annually in the USA, but only an estimated 10 to 20% of all cases are reported. Other infections, including salmonellosis, giardiasis, amebiasis, shigellosis, campylobacteriosis, hepatitis A and B, and cytomegalovirus infection, are transmitted sexually but also by other routes. A strong association between cervical cancer (see Ch. 241) and sexually transmitted papillomaviruses exists. Since 1978, HIV has spread rapidly among various populations (see Ch. 163).

STD incidence rates remain high in most of the world, despite diagnostic and therapeutic advances that can rapidly render patients with many STDs noninfectious and cure most. In many cultures, changing sexual mores and oral contraceptive use have elim-

hemolytic streptococcus; however, because nephrogenic strains of streptococci are less prevalent, nephritis is less common.

Treatment

Application of mupirocin ointment 3 times daily has been effective in treating impetigo caused by *S. aureus* and group A β-hemolytic streptococcus, although some resistant strains have developed. Patients showing no response to mupirocin in 3 to 5 days should be treated systemically. Because most cases are caused by penicillinase-producing staphylococci, cloxacillin or a 1st-generation cephalosporin is the drug of choice. Penicillin-allergic patients should receive cefadroxil 30 mg/kg/day po divided in 2 daily doses or cephalexin for 10 days (50 mg/kg/day po divided q 6 h for children, 250 mg qid for adults) rather than erythromycin; the increased frequency of erythromycin-resistant staphylococci (10 to 40%) has decreased the drug's effectiveness. Most streptococci are sensitive to erythromycin but rarely to tetracycline. In pure staphylococcal pyoderma, a penicillinase-resistant penicillin (eg, cloxacillin 50 mg/kg/day po divided q 6 h for children or 250 mg qid for adults) should be given for 10 days.

In secondary impetigo or ecthyma, the underlying condition must also be treated.

VIRAL INFECTIONS

(For a summary of differential diagnosis of the more common exanthems, see TABLE 265–8.)

MEASLES

(Rubeola; Morbilli; Nine-Day Measles)

A highly contagious, acute viral infection characterized by fever, cough, coryza, conjunctivitis, enanthem (Koplik's spots) on the buccal or labial mucosa, and a spreading maculopapular cutaneous rash.

Etiology and Pathogenesis

Measles is caused by a paramyxovirus. Measles (like chickenpox) is extremely communicable and is spread mainly by small droplets from the nose, throat, and mouth of a person in the prodromal or an early eruptive stage of the disease or by airborne droplet nuclei. Indirect spread by uninfected persons or by objects is unusual. The communicable period of the disease begins 2 to 4 days before the rash appears until 2 to 5 days after onset. The virus disappears from nose and throat secretions by the time the rash clears. Persons who develop mild desquamation after the rash are no longer infectious.

Atypical measles syndrome usually occurs in persons previously immunized with the original killed virus measles vaccines, which are no longer available. Presumably, inactivated measles virus vaccines do not prevent wild virus infection and can sensitize patients so that disease expression is altered significantly. However, atypical measles syndrome may also follow immunization with live, attenuated measles vaccine, perhaps resulting from inadvertent inactivation due to improper storage.

Epidemiology

Before widespread immunization, measles epidemics occurred every 2 or 3 yr, with small localized outbreaks during intervening years. In recent years in the USA, outbreaks have occurred most commonly in previously immunized adolescents and young adults and sometimes in unimmunized preschool-aged children. An infant whose mother has had measles receives transplacental passive immunity lasting most of the first year of life; thereafter, susceptibility is high. One attack of measles confers lifelong immunity.

Symptoms and Signs

Typical measles begins, after a 7- to 14-day incubation period, with prodromal fever, coryza, hacking cough, and conjunctivitis. The pathognomonic Koplik's spots appear 2 to 4 days later, usually on the buccal mucosa opposite the 1st and 2nd upper molars. These spots resemble tiny grains of white sand surrounded by inflammatory areolae. If they are numerous, the entire background may be a mottled erythema. Pharyngitis and inflammation of the laryngeal and tracheobronchial mucosa develop. Characteristic multinucleated giant cells appear in nasal secretions, pharyngeal and buccal mucosa, and, often, urinary sediment.

The characteristic rash appears 3 to 5 days after onset of symptoms, usually 1 to 2 days after Koplik's spots appear. It begins in front of and below the ears and on the side of the neck as irregular macul
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Koplik's spots appear. It begins in front
d below the ears and on the side of the neck as irregular macules that soon become maculopapular and spread rapidly (within 24 to 48 h) to the trunk and extremities, as they begin to fade on the face. Petechiae or ecchymoses may occur with particularly severe rashes.

At the peak of the illness, the temperature may exceed 40° C (104° F), with periorbital edema, conjunctivitis, photophobia, a hacking cough, extensive rash, and mild itching; generally, the patient appears quite ill. Leukopenia with a relative lymphocytosis is usual. The constitutional symptoms and signs parallel the severity of the eruption and vary with the epidemic. In 3-to-5 days, the fever falls, the patient feels more comfortable, and the rash begins to fade rapidly, leaving a coppery-brown discoloration followed by desquamation.

Atypical measles syndrome may begin abruptly, with high fever, toxicity, headache, abdominal pain, and cough. The rash may appear 1 to 2 days later, often beginning on the extremities, and may be maculopapular, vesicular, urticarial, or purpuric. Edema of the hands and feet may occur. Pneumonia and hilar adenopathy are common, and nodular densities in the lungs may persist for ≥ 12 wk. Moderate to severe abnormalities in the ventilation/perfusion ratio in the lungs may cause significant hypoxemia.

Complications

Bacterial superinfections occur commonly (in addition to the typical respiratory tract involvement of measles), causing pneumonia, otitis media, and other suppurative infections. Measles causes transient suppression of delayed hypersensitivity, leading to a transient reversal of previously positive tuberculin and histoplasmin skin tests and sometimes to worsening of active TB or reactivation of latent TB. An exacerbation of fever, change in WBC count from leukopenia to leukocytosis, and malaise, pain, or prostration suggest a complicating bacterial infection. Immunocompromised patients may develop a severe, progressive giant cell pneumonia without a rash.

Acute thrombocytopenic purpura, at times with severe hemorrhagic manifestations, may complicate the acute phase of measles.

Encephalitis occurs about once in 1000 to 2000 cases, usually 2 days to 3 wk after onset of the rash, often beginning with high fever, convulsions, and coma. In most cases, the CSF lymphocyte count is between 50 and 500/μL and the protein level is mildly increased. A normal CSF at the time of initial symptoms does not rule out encephalitis. The course may be brief, with recovery in about a week, or may be prolonged, terminating in serious CNS impairment or death.

Subacute sclerosing panencephalitis (SSPE) is also associated with measles virus and is discussed below.

Diagnosis

Typical measles may be suspected in a patient with a history of measles exposure and coryza, photophobia, and evidence of bronchitis, but before the rash appears a definite diagnosis can be made only by identifying Koplik's spots. In most cases, these spots, followed by high fever, malaise, and the rash with its characteristic cephalocaudal progression, establish the diagnosis. Although it is rarely necessary, the virus can be detected early by rapid immunofluorescent staining of pharyngeal and urinary epithelial cells or can be grown in tissue culture; it is easier to detect, however, by demonstrating a rise in antibody levels between acute and convalescent sera.

Differential diagnosis of typical measles includes rubella, scarlet fever, drug rashes, serum sickness, roseola infantum, infectious mononucleosis, adenovirus, and echo- and coxsackievirus infections (see TABLE 265–8). Distinguishing features of rubella include its mild course with few or no constitutional symptoms, enlarged (and usually tender) postauricular and suboccipital lymph nodes, low-grade fever, normal WBC count, usual absence of a recognizable prodrome, and short duration. **Scarlet fever** may be suggested at first by the pharyngitis and fever, but the leukocytosis of scarlet fever is absent in measles and the rash is morphologically distinct. **Drug rashes** (eg, from phenobarbital or sulfonamides) resemble the measles rash, but again, the typical prodrome, cough, and cephalocaudal progression of the rash are absent, and the palms and soles are more likely to be prominently involved. Here, especially, the history is important. **Roseola infantum** can produce a skin rash similar to that of measles but is seldom seen in children > 3 yr. It can usually be differentiated by its high initial temperature, absence of Koplik's spots and malaise,

TABLE 265–8. DIFFERENTIAL DIAGNOSIS OF THE MORE COMMON EXANTHEMS

Condition	Incubation (days)	Period of Communicability	Symptoms and Signs	Eruption			Laboratory Findings
				Site	Character	Onset; Duration	
Measles (rubeola)	7–14	From 2–4 days before appearance of rash until 2–5 days after onset	Koplik's spots, fever, coryza, cough, conjunctivitis, photophobia, usually mild pruritus	Starts around ears and on face and neck, spreads over trunk and limbs; limbs escape in mild cases	Maculopapular, brownish pink, and irregularly confluent in severe cases, or even petechial; discrete in mild cases	3–5 days after onset of symptoms; lasts 4–7 days	Granulocytic leukopenia; virus in blood and nasopharynx
Rubella (German measles)	14–21	From 1 wk before onset of symptoms until rash disappears	Malaise, fever, headache, rhinitis, postauricular and suboccipital lymphadenopathy with tender nodes	Face and neck, spreads to trunk and limbs	Fine pinkish macules that become confluent and often scarlatiniform or pinpoint on 2nd day	1 or 2 days after onset of symptoms; lasts 1–3 days	WBC count usually normal or slightly reduced; virus in blood and nasopharynx
Roseola infantum (exanthem subitum, human herpesvirus 6 infection)	Probably 5–15	Unknown	Characteristic disappearance of high fever and simultaneous appearance of rash in infants and preschool children, risk of seizures	Chest and abdomen, with moderate involvement of face and extremities	Diffuse macular or maculopapular	On about 4th day after onset of symptoms, rash appears as temperature drops rapidly to normal; lasts 1–2 days	Granulocytic leukopenia
Erythema infectiosum (fifth disease)	4–14	From before onset of rash until rash develops (unlikely to be infectious after onset of rash)	Low-grade fever, occasional arthralgias	Starts on cheeks, spreads to arms, legs, trunk	Maculopapular; often blotchy or reticular	Shortly after onset of symptoms; lasts 5–10 days; may recur for several weeks	Mild lymphocytosis and eosinophilia
Chickenpox (varicella)	10–21	From a few days before onset of symptoms until all crops of vesicles have crusted	Moderate fever, headache, malaise, occasional sore throat	Usually 1st on trunk, later on face, neck, extremities; infrequently on palms and soles	Lesions discrete; progress from macule to papule to vesicle to crusting; appear in crops, hence various	Shortly after onset of symptoms; lasts a few days to 2 wk	Presence of virus in vesicle fluid by immunofluorescent staining; or multinucleated

herpesvirus 6 infection)			appearance of rash in infants and preschool children, risk of seizures	and extremities		appears as temperature drops rapidly to normal; lasts 1–2 days	
Erythema infectiosum (fifth disease)	4–14	From before onset of rash until rash develops (unlikely to be infectious after onset of rash)	Low-grade fever, occasional arthralgias	Starts on cheeks, spreads to arms, legs, trunk	Maculopapular; often blotchy or reticular	Shortly after onset of symptoms; lasts 5–10 days; may recur for several weeks	Mild lymphocytosis and eosinophilia
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Infectious mononucleosis	10–50	Undetermined	Malaise, headache, fever, sore throat, splenomegaly, generalized lymphadenopathy	Most prominent over trunk	Occurs in about 15% of cases as a morbilliform, scarlatiniform, or vesicular rash, often in association with antibiotics	5–14 days after onset of illness; lasts 3–7 days	Positive heterophil antibody test; leukocytosis with atypical enlarged lymphocytes, appearance of antibodies to Epstein-Barr virus
Scarlet fever (scarlatina)	3–5 (occasionally slightly shorter or longer)	Usually from 24 h before onset of symptoms until 2–3 wk after or longer if complications occur (eg, sinusitis, otitis media)	Sore throat, chills, fever, headache, vomiting, strawberry tongue, cervical lymphadenopathy, circumoral pallor, rapid pulse	Face, neck, chest, abdomen, and spreads to extremities; entire body surface may be involved	Diffuse pinkish red flush of skin, blanches on pressure	On 2nd day; lasts 4–10 days	Granulocytosis; throat culture positive for β-hemolytic streptococcus
Drug rash	Variable—depends on history of recent drug use	None	Variable, including fever, malaise, arthralgia, nausea, photophobia, pruritus	Generalized; sometimes restricted to exposed surfaces	May be morbilliform, scarlatiniform, erythematous, acneiform, vesicular, bullous, purpuric, exfoliating	Variable	Agranulocytosis or eosinophilia possible; presence of drug in urine

and rash appearing simultaneously with defervescence.

Differential diagnosis of atypical measles syndrome is similar to that of typical measles; however, the pleomorphism of the rash and the severe constitutional signs sometimes observed may suggest Rocky Mountain spotted fever, leptospirosis, hemorrhagic varicella, or meningococcal infection; other differential diagnoses include certain bacterial or viral pneumonias, collagen vascular diseases such as juvenile RA, and Kawasaki syndrome (mucocutaneous lymph node syndrome). A history of measles exposure and prior administration of killed virus vaccine suggest the diagnosis, but virus isolation, serologic studies, or both may be necessary to confirm it.

Prognosis and Prophylaxis

In healthy, well-nourished children, measles has a low mortality rate unless complications ensue.

A live attenuated virus vaccine can provide long-lasting immunity. The vaccine produces mild, or inapparent, noncommunicable infection and an antibody response similar to that of natural measles. Fever > 38° C (> 101° F) occurs 5 to 12 days after inoculation in < 5% of vaccinees and is often followed by a rash. CNS reactions are exceedingly rare. For routine immunization, see CHILDHOOD IMMUNIZATIONS in Ch. 256.

Exposed susceptible contacts may be protected if the live vaccine is given within 2 days of exposure. Alternatively (eg, in pregnant patients and children < 1 yr), measles immune globulin (MIG) or immune serum globulin 0.25 mL/kg IM is given immediately. This is followed by vaccination in 5 to 6 mo if medically appropriate (eg, patient no longer pregnant, child now > 1 yr). Simultaneous administration of MIG or immune serum globulin with the vaccine is contraindicated. An exposed susceptible patient with a condition that contraindicates use of any live measles virus vaccine (see below) is given MIG or immune serum globulin 0.5 mL/kg IM (maximum, 15 mL). If such an immunocompromised patient also has a bleeding disorder (eg, thrombocytopenia), IV globulin should be considered.

Contraindications to the use of any live measles virus vaccine include generalized malignancies (eg, leukemia, lymphoma), immunodeficiency diseases, and therapy with corticosteroids, irradiation, alkylating agents, or antimetabolites. Reasons to defer vaccination include pregnancy, any acute febrile illness, active untreated TB, or administration of antibody (as whole blood, plasma, or any immune globulin) within the preceding 8 wk.

In HIV-infected children and infants, the live measles vaccine is recommended for those with and without symptoms but who are not severely immunocompromised. In these children, the risk of severe or lethal measles infection outweighs the theoretical risk of vaccine-associated measles. There has been a case of measles caused by a vaccine strain in a child with advanced HIV disease, so the vaccine should not be given to severely immunocompromised HIV-infected children with low proportional or absolute CD4 counts.

Treatment

Treatment is symptomatic. Secondary bacterial infections require appropriate antimicrobial drugs. Vitamin A reduces morbidity and mortality in malnourished children with severe measles. For children > 1 yr, vitamin A 200,000 IU po should be administered for 2 days (total dose, 400,000 IU) if the child has ophthalmologic evidence of vitamin A deficiency and repeated in 4 wk. Children without ophthalmologic evidence of vitamin A deficiency receive a single dose of 200,000 IU. Children 6 mo to 1 yr should receive a dose of 100,000 IU. Immune serum globulin is ineffective in encephalitis; symptomatic care is the only treatment available.

SUBACUTE SCLEROSING PANENCEPHALITIS

A progressive, usually fatal, brain disorder occurring months to usually years after an attack of measles and characterized by mental deterioration, myoclonic jerks, and seizures.

Etiology and Epidemiology

Subacute sclerosing panencephalitis (SSPE) is thought to represent a persistent measles virus infection. Measles virus has been demonstrated in brain tissue by electron microscopy and isolated from brain biopsies; measles antigen has been demonstrated in brain tissue by fluorescent antibody techniques. SSPE has been reported in children who did n
of natural measles but who
sles vaccine, although som
may have resulted from un
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SSPE occurs in about 6 t
cases of measles. With vac
lower, at about 1 case per
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Onset is usually before age
ceedingly rare in the USA a
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Symptoms and Signs

SSPE causes intellectua
convulsive seizures, and m
ties. Often, the first signs are
formance in schoolwork, for
per outbursts, distractibility
and hallucinations. Seizures
tal changes and initially are
Grand mal seizures may
show further intellectual dec
speech, and abnormal inv
ments. Dystonic movement
periods of opisthotonos occu
of the body musculature, di
lowing, cortical blindness, a
may occur. Focal chorioret
funduscopic abnormalities
patients. In the final phases,
comes increasingly rigid, w
signs of hypothalamic invol
perthermia, diaphoresis, and
pulse and BP).

The disease, almost invari
1 to 3 yr (often as the result o
monia), sometimes has a n
course, with pronounced neu
A few patients have remissi
bations.

Diagnosis

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curring synchronously thro
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CSF usually is under norma
has a normal cell count and
The CSF globulin is almost al
elevated and may constitute
to 60% of the total CSF prot
and CSF contain elevated le

ISED BY ENTEROVIRUSES

ted	Comments
10; id	Most common in infants and children; characteristic palatal and pharyngeal lesions
us	Most common in young children; vesicular exanthem usually brief and benign
	Most common in children but may affect any age group
}, id,	Most common in infants and children; course usually benign
ses l	Transient mild paresis with aseptic meningitis may occur at any age; younger children generally have milder disease
	May occur at any age; myocarditis neonatorum has high mortality
:	May occur at any age
},	Course usually benign
	Course usually benign
	Most common in infants and children; course usually mild
	Probably most important in newborns or preterm infants
	Outbreaks of hemorrhagic conjunctivitis most common with enterovirus 70; mild or inapparent cases may be more likely in children

and host characteristics that variably overlap with coxsackieviruses and echoviruses).

Coxsackieviruses and echoviruses (*enteric cytopathic human orphan*) are antigenically heterogeneous. They have been isolated from oral secretions, stool, blood, and CSF and have wide geographic distribution. They resemble polioviruses in size, resistance to physical and chemical agents, prevalence during summer and fall, and chiefly person-to-person spread. Enteroviruses cause a wide variety of syndromes (see TABLE 265–11).

Poliomyelitis

(Infantile Paralysis; Acute Anterior Poliomyelitis)

Acute viral infection caused by poliovirus, producing nonspecific minor illness, aseptic meningitis (nonparalytic poliomyelitis), and flaccid weakness of various muscle groups (paralytic poliomyelitis).

Etiology and Epidemiology

Poliovirus is small (22 to 30 nm), with a single-stranded RNA genome and no envelope. Of the three serotypes, type 1 is the most paralytogenic and the most common cause of epidemics.

Humans are the only natural hosts for polioviruses. Infection occurs through direct contact and is highly contagious. Inapparent infections (the main source of spread) are common in nonimmunized populations, but overt disease is rare; even in epidemics, the ratio of inapparent infections to clinical cases is > 100:1. Paralytic disease was thought to be uncommon in developing (mainly tropical) countries, but before introduction of vaccines its incidence was as high as in the peak years in the USA. In such areas, where sanitation and hygiene are poor, virus circulation is extensive and occurs yearround, infection and immunity are acquired in the first few years of life, there are no epidemics, and > 90% of paralytic cases occur in children < 5 yr. In contrast, as sanitation and hygiene improved in economically developed countries, infection was delayed, many older children and young adults remained susceptible, and summer epidemics occurred in increasingly older patients. Extensive vaccination has almost eliminated the disease in developed countries. Poliomyelitis may soon be eradicated worldwide.

Pathology and Pathogenesis

Virus enters the mouth, and primary multiplication occurs in lymphoid tissues in the oropharynx and GI tract, mainly the ileum. Small amounts of virus reach the blood and are carried to other sites in the reticuloendothelial system, where extensive multiplication occurs. Secondary viremia is followed by invasion of the CNS. Virus may sometimes reach the CNS via peripheral nerve fiber endings. The virus is present in the throat and feces during incubation and, after symptom onset, persists for 1 to 2 wk in the throat and for ≥ 3 to 6 wk in feces. Viremia lasts several days but disappears with symptom onset, when antibodies have already developed.

Significant virus-induced pathology occurs in only the spinal cord and brain, involving the motor neurons of the anterior horn of the spinal cord; the medulla; and, to a lesser degree, other parts of the brain, including the cerebellum and the motor cortex. Damage to neurons by the virus, the primary event, elicits an intense inflammatory reaction and eventually neuronophagia. The site and severity of paralysis are determined by the distribution of the neuronal lesions. Factors predisposing to serious neurologic damage include increasing age (throughout life), recent tonsillectomy or inoculation (most often DTP), pregnancy, and physical exertion concurrent with onset of the CNS phase.

Symptoms and Signs

Clinical forms vary, but the basic patterns are minor illness (abortive) and major illness (paralytic or nonparalytic).

Minor poliomyelitis accounts for 80 to 90% of symptomatic infections, occurs chiefly in young children, is mild, and does not involve the CNS. Symptoms are slight fever, malaise, headache, sore throat, and vomiting, which develop 3 to 5 days after exposure. Recovery occurs in 24 to 72 h.

Major poliomyelitis may follow several days of well-being after a minor illness but more commonly has no preceding minor illness, especially in older children and adults. Incubation is usually 7 to 14 days; rarely, longer. Fever, severe headache, stiff neck and back, deep muscle pain, and sometimes hyperesthesias and paresthesias may occur.

During active myelitis, urinary retention and muscle spasms are common. There may be no further progression, but loss of certain tendon reflexes and asymmetric weakness or paralysis of muscle groups may develop, depending on the location of lesions in the spinal cord or medulla. Respiratory failure may result from spinal cord involvement causing paralysis of the respiratory muscles or from viral damage to the respiratory centers in the medulla and paralysis of muscles innervated by the cranial nerves. Dysphagia, nasal regurgitation, and nasal voice are early signs of bulbar involvement. Encephalitic signs occasionally predominate. CSF glucose is normal, protein is slightly elevated, and the cell count is commonly 10 to 300/μL (predominantly lymphocytes). The peripheral WBC count may be normal or moderately increased.

Diagnosis

Asymmetric flaccid limb paralysis or bulbar palsies without sensory loss during an acute febrile illness in a child or young adult almost always indicates poliomyelitis. Although, rarely, certain group A and B coxsackieviruses (especially A7), several echoviruses, and enterovirus type 71 may produce muscle weakness or paralysis that cannot be clinically differentiated from paralytic poliomyelitis. The causative virus can be identified by laboratory tests; treatment is the same as for paralytic poliomyelitis. Guillain-Barré syndrome (see in Ch. 183) is often confused with paralytic poliomyelitis but usually produces no fever, muscle weakness is symmetric, sensory findings coexist in 70% of cases, and CSF protein is usually elevated with a normal cell count. CNS involvement due to mumps or herpesviruses, meningoencephalitis due to arboviruses in certain geographic areas, tuberculous meningitis, or brain abscess should also be considered. Nonparalytic poliomyelitis cannot be differentiated clinically from aseptic meningitis due to other agents; the diagnosis is confirmed by isolating the virus from the throat or feces or demonstrating a rise in specific antibody titer.

Prognosis

In minor and nonparalytic major forms, recovery is complete. In paralytic poliomyelitis, < 25% of patients have severe permanent disability, about 25% have mild disabilities, and > 50% recover with no residual paralysis. The return of muscle function is greatest in the first 6 mo, but improvement may continue for 2 yr. Mortality is 1 to 4% but increases to 10% in adults and in those with bulbar disease.

A **postpoliomyelitis syndrome**—muscle fatigue and decreased endurance, often accompanied by weakness, fasciculations, and atrophy in selective muscles—may occur many years after paralytic poliomyelitis, particularly in older patients and in those more severely affected initially. The cause may be related to further loss of anterior horn cells due to aging in a population of neurons already depleted by earlier poliovirus infection.

Prophylaxis

All infants and children should be immunized (see CHILDHOOD IMMUNIZATIONS in Ch. 256) with Sabin live attenuated oral polio vaccine (OPV) or Salk inactivated poliovirus vaccine (IPV), the latter now available in an enhanced form that evokes a more potent antibody response given as a series of injections with periodic booster doses. OPV and IPV induce circulating antibodies, but OPV also induces alimentary tract resistance associated with local secretory antibody production (IgA) that blocks virus implantation. Very rarely, OPV has been associated with paralytic poliomyelitis. OPV is contraindicated in immunodeficient patients, who should receive IPV, and in families with an immunodeficient member because of the possibility of contact infection from vaccinees who excrete the virus. From 1980 to 1994, 124 cases of vaccine-associated paralytic poliomyelitis were reported: 39% occurred in otherwise healthy vaccinees, usually after the first dose; 32% occurred in healthy contacts (mostly adults) of vaccinees; 24% occurred in vaccinees and contacts of vaccinees with abnormal immune systems; and the remainder occurred in persons with no history of recent vaccination and no known contact with a vaccinee. Because of the rare but possibly preventable cases of vaccine-associated poliomyelitis in the USA, the American Academy of Pediatrics recommends three options: the traditional schedule (OPV given at 2 mo, 4 mo, and 6 to 18 mo and a booster dose at 4 to 6 yr); an inactivated poliovirus-only schedule (IPV given at 2 mo, 3 to 4 mo, and 9 to 16 mo

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Treatment

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only bed rest for s
antipyretics may
During active
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is indicated. UTI
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both types. Post
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ryngeal muscle w
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and a booster dose at 4 to 6 yr); and a sequential schedule (IPV given at 2 and 4 mo, followed by OPV given at 12 to 18 mo and at 4 to 6 yr). Primary vaccination of adults is not routinely recommended in the USA. However, nonimmunized adults traveling to endemic or epidemic areas should be given at least one dose of IPV or trivalent OPV.

Treatment

Therapy is symptomatic. Patients with minor or mild nonparalytic major forms need only bed rest for several days. Analgesics and antipyretics may be useful.

During active myelitis, rest on a firm bed (with footboards to help prevent footdrop) is indicated. UTI due to urinary dysmotility should be treated with an appropriate antibiotic, and high fluid intake helps to prevent formation of urinary calcium phosphate calculi. Physical therapy is the most important part of management during convalescence.

Artificial respiration is the treatment for both types. Postural drainage and suction should be instituted in patients with pharyngeal muscle weakness, difficulty in swallowing, inability to cough, and pooling of bronchotracheal secretions. Intubation or tracheostomy is frequently required to keep the airway clear. Pulmonary atelectasis is common, and bronchoscopy and suction are often necessary. For further details regarding respiratory intensive care, see Ch. 66. Antimicrobial drugs are not recommended unless bacterial infection occurs.

Herpangina

An acute infectious febrile disorder caused by numerous group A coxsackieviruses and occasionally other enteroviruses and characterized by vesiculoulcerative mucosal lesions.

Herpangina tends to occur in epidemics, most commonly in infants and children, and is characterized by sudden onset of fever with sore throat, headache, anorexia, and, frequently, pain in the neck, abdomen, and extremities. Vomiting and convulsions may occur in infants. Within 2 days after onset, a few (rarely > 12) small (diameter 1 to 2 mm) grayish papulovesicular lesions with erythematous areolae appear, most frequently on the tonsillar pillars but also on the soft palate, tonsils, uvula, or tongue. During the next 24 h, the lesions become shallow ulcers, seldom > 5 mm in diameter, that heal in 1 to 5 days. Complications are unusual, and the patient is generally asymptomatic by day 7. Lasting immunity to the infecting strain follows, but repeated episodes caused by other group A coxsackieviruses or other enteroviruses are possible.

Diagnosis is based on the symptoms and characteristic oral lesions. It is best confirmed by isolating the virus from the lesions or by demonstrating a rise in specific antibody titer, but such testing is not routinely recommended. Differential diagnosis includes herpetic stomatitis (which occurs during any season and is characterized by larger, more persistent ulcers), recurrent aphthae, and Bednar's aphthae (which rarely occur in the pharynx and generally are not associated with systemic symptoms). Coxsackievirus A10 causes a similar disease (lymphonodular pharyngitis), but oral and pharyngeal lesions are raised, whitish to yellowish nodules. Treatment is symptomatic.

Hand-Foot-and-Mouth Disease

An acute infectious febrile disorder usually caused by coxsackievirus A16 and characterized by a vesicular exanthem of skin and mucosa.

The disease is most common among young children. The course is similar to that of herpangina, but a vesicular exanthem is distributed over the buccal mucosa and palate, with similar lesions appearing on the hands and feet and occasionally in the diaper area. Treatment is symptomatic.

Epidemic Pleurodynia

(Bornholm Disease)

An acute infectious febrile disorder caused by a group B coxsackievirus and characterized by severe epigastric or thoracic pain.

Epidemic pleurodynia may occur at any age but is most common in children. There is sudden onset of severe, frequently intermittent, often pleuritic pain in the epigastrium or lower anterior chest, with fever and often headache, sore throat, and malaise. Local tenderness, hyperesthesia, muscle swelling, and myalgias of the trunk and extremities may occur. The disease usually subsides in 2 to 4 days, but relapse may occur within a few days and symptoms may continue or recur for several weeks. Up to 5% of cases

AN INVESTIGATION INTO THE EFFICACY OF *OCIMUM GRATISSIMUM* AS USED IN NIGERIAN NATIVE MEDICINE

By F. El-Said, E. A. Sofowora, S. A. Malcolm, and Miss A. Hofer[1]

Six species of *Ocimum* (*Labiatae*) have been described in the Flora of West Tropial Africa (Hutchinson and Dalziel, 1963): *O. bisilicum* L., *O. canum Sims*, *O. gratissimum*, L., *O. irvinei* Morton, *O. lannifolum* Hochstex Benth. and *O. suave* Willd.

In Nigeria, a decoction of the leaves of *O. gratissimum* is used in the treatment of fever, as a diaphoretic and also as a stomachic and laxative (Oliver, 1960). In Francophone West Africa, the plant is used in treating coughs and fevers and as an anthelmintic (Oliver, 1960).

In areas around Ibadan (Western State of Nigeria), *O. gratissimum* is most often taken as a decoction of the whole herb (*Agbo*) and is particularly used in treating diarrhoea. Various species of *Ocimum* have been reported to contain eugenol (*Yeh*, 1960) while *O. gratissimum* was reported to contain thymol also (Oliver, 1960). The essential oil of *O. gratissimum*, like that of *O. basilicum*, was found to posses some antibacterial properties; the vapour of this oil was also reported to kill protozoa (Tokin, 1943).

However, *O. gratissimum* thrives in Nigeria and is widely cultivated in the Western State to make it readily available for medicinal use. In order to obtain a more accurate measure of its efficacy in local usage, the aqueous extracts and the essential oil of the plant, and also a decoction made according to local practice have been tested in this laboratory.

Also the yield of essential oil from the Ibadan specimens of *O. gratissimum* as well as its analysis have been determined and compared with those of other geographical sources reported in the literature.

Experimental and Results

Materials and Authentication

All *Ocimum gratissimum* specimens used were collected from areas around Ibadan (Western State of Nigeria) and the identity of each batch was confirmed by comparison with known specimens at the Forest Research Department's herbarium in Ibadan, Western State of Nigeria.

Determination of Moisture content

The moisture content was determined by accurately weighing duplicate (5–8 g) samples of the plant or plant part. The loss in weight after drying for 16 hours at 100° C was used to calculate the moisture content. Fresh leaves contained 70–80% moisture, while fresh inflorescences contained 60–75% moisture.

[1] Peace Corps Volunteer.

Volatile oil contents

The British Pharmacopoeia Method I (1963) involving steam distillation, was used for the estimation of volatile oil content, using 50 g of fresh coarsely-chopped plant. The oil content was calculated as mls of oil collected per 100 g of the sample on a moisture – free basis (m. f. b.).

The results for the determinations on the leaf and the inflorescence are summarised in Table 1. Only a trace of volatile oil was obtained from the stems.

Table 1: Yield of essential oils for Ibadan Specimens of *Ocimum gratissimum*

Specimen No.	Source	Oil content % m. f. b.	
		Leaf	Inflorescence
1.	Ibadan North	3.2	1.5
2.	„ „	3.2	0.5
3.	„ „	4.1	1.2
4.	„ „	3.9	1.4
5.	Ibadan South	3.5	0.9
6.	„ „	3.8	0.7

Determination of physical constants of the oil

The refractive index was determined at room temperature (25° C) using an Abbé refractometer. The optical rotation of the essential oil obtained from the fresh leaves of O. *gratissimum* was measured with a Bellingham and Stanley polarimeter using a 2 decimeter tube with a 16% w/v solution of the oil in chloroform. The optical rotation was 0.0 ± 0.2. The refractive index (n^{25}) of the essential oil of O. *gratissimum* was 1.4932 (leaves), 1.4982 (inflorescence) and 1.4959 (whole herb).

Thin-layer chromatography of essential oils

The essential oil of O. *gratissimum* leaves was co-chromatographed with eugenol and thymol on 0.25 mm thick silica gel plates (Stahl, 1965) using a mixture of n-hexane: diethyl ether (4:1) as the developing solvent. The solvent front was allowed to run 12 cm. Both the thymol and eugenol spots gave a dark grey fluorescence when viewed under ultraviolet light. The following R_F values were obtained for two such chromatograms.

Table 2: Thin-layer Chromatography of the essential oils of O. *gratissimum*

Specimen	R_F		
	Plate 1	Plate 2	Mean
Eugenol	0.48	0.45	0.46
O. *gratissimum*	0.59	0.57	0.58
Thymol	0.63	0.67	0.65

Gas-chromatography of the essential oils

0.1 µl samples of the specimens were introduced into the Aerograph 1520 gas-chromatograph fitted with an ethylene glycol column and a flame ionisation detector. The following operational conditions were used:

Carrier gas (N_2) pressure	40 p. s. i	Sensitivity	10
Carrier flow	8 mls/min	Attenuation	4
Hydrogen (flame) flow	20 mls/min	Chart speed	40 ins/hr
Column temperature	150° C		

The retention time for thymol under these conditions was 4 mins 25 secs, while that for eugenol was 5 min 50 secs. The gas chromatograms of the essential oils from the leaf, the inflorescence and from the herb showed five distinct peaks for each oil. The major peak corresponded to thymol (50% or more) in each oil.

Anti-bacterial activity

(a) Extract of the whole herb

(i) An aqueous extract of 50 g of the dried and powdered whole herb was prepared by refluxing for 2 hours with 200 mls of water and then filtering.

(ii) An aqueous decoction was prepared as follows: the fresh whole herb was packed into a covered vessel, sufficient water was added to cover the herb and the whole was boiled for 1 hour. The supernatant was then decanted. (This is the method by which extracts are prepared locally).

Testing of the extracts

20 ml of nutrient agar was poured into a petri dish and allowed to set. Using a sterile scalpel, a "ditch" (1 cm wide) was cut across the plate and the extract was filled into the ditch. Cultures of various organisms were then spread across the plate at right angles to the ditch. The plate was incubated at 37° for 24 hours and then examined for inhibition of growth.

The organisms used were *Salmonella* spp, *Escherichia coli, Shigella sonnei* and *Shigella schmitzi*. Neither of the extracts tested showed inhibitory activity against any of the organisms used.

(b) Anti-bacterial activity of the oil of O. gratissimum

Preliminary investigations of anti-bacterial activity were made by placing small drops of the oil on the surface of seeded agar plates, incubating and examining for zones of inhibition. The organisms used were as follows:

Gram-negative		Gram-positive
Escherichia coli	*Salmonella spp.*	*Bacillus subtilis*
Klebsiella aerogenes	*Shigella schmitzi*	*Sarcina lutea*
Proteus spp.	*Shigella sonnei*	*Staphylococcus aureus*
Pseudomonas aeruginosa		

With the exception of *Ps. aeruginosa*, against which the oil showed no activity, zones of inhibition were obtained for all organisms.

(c) Anti-bacterial activity of aqueous solutions of the oil of O. gratissimum

A solution of the oil in water was made by shaking 0.5 ml of the oil with 200 ml of sterile water at intervals over a period of 48 hours and at an ambient temperature of approximately 30°. The excess oil was removed by filtration.

Serial dilutions of the aqueous solution were made in nutrient broth. Each dilution was inoculated with 0.2 ml of a 24 hours broth culture of the appropriate organism and incubated at 37° for 7 days. At the end of the incubation period the dilutions were examined for growth. The results, expressed as the minimum percentage saturation of the broth with oil required to inhibit growth, are given in Table 3.

For these purposes the original solution was considered to be saturated with the oil. For purposes of comparison, a saturated aqueous solution of thymol was prepared and its activity determined in the same manner as with the aqueous solution of oil. The results obtained, expressed as the minimum percentage saturation of broth with thymol required to inhibit growth, are also shown in Table 3.

Table 3

Organism	Minimum inhibitory % Saturation	
	Oil of *O. gratissimum*	Thymol
Ps. aeruginosa	>75	>75
Salmonella spp	27.5	20.0
E. coli	25.0	17.5
Staph. aureus	25.0	17.5
Shigella sonnei	24.0	12.5
Shigella schmitzi	20.0	11.0

Thymol was found to be more active than the oil of *O. gratissimum* but neither aqueous solutions of thymol nor of *O. gratissimum* oil had any appreciable activity against *Ps. aeruginosa*.

Discussion

Preliminary investigation of *Ocimum gratissimum* showed that the plant contained mainly essential oils and non-phlobatanins. The essential oil content of the *Ocimum gratissimum* from Ibadan appears to be relatively high. It ranged from 3.2% to 4.1% (m.f.b) for fresh leaves and from 0.5% to 1.4% for the fresh inflorescence.

Although no values could be found for the essential oil content of *O. gratissi-*

mum leaves and inflorescence separately in the literature, figures ranging from 0.38% to 0.53% have been reported for the yield of essential oil in the whole herb. Of course, these figures include the stem, which contains only a trace of oil.

A 'high yielding' cross of *O. gratissimum* and *O. menthaefolium* was reported to produce 0.15 to 0.29 mls of oil per 100 g fresh leaves (Kostecka, 1964). This represents only 0.60–1.2%, moisture-free (allowing for 75% moisture) – a value which is considerably less than the yield for Ibadan specimens of *O. gratissimum*.

The wide variation in the yield of volatile oil by the inflorescence (Table 1) may be due to variation in the stage of the development of component florets of any *O. gratissimum* plant, although efforts were made to attain uniformity in sampling. The refractive index of the oils obtained from the leaves, inflorescence, stem and whole herb were very close and within the range already reported in the literature for *O. gratissimum*. The oils were, however, not optically active while the oil obtained from *O. gratissimum* in Formosa was laevorotatory – $[\alpha]_D^{25} - 12.4°$ – (Wang, 1948).

It was found that among various other solvent mixtures tested, a mixture of n-hexane : diethyl ether (4 : 1) was most satisfactory for separating eugenol and thymol on silica gel plates. This served as a quick method of determining whether the essential oil from the plant contained thymol and/or eugenol.

No eugenol could be detected from any of the *O. gratissimum* oils tested by T.L.C. The R_F values obtained for the thymol in the oils were a little low probably because it is present in a mixture. That the oil produced mainly thymol and very little eugenol was confirmed by gas-chromatography because at the normal sensitivity of 10, eugenol was not detectable in any of the oils. Only when the sensitivity was increased 100 times it was possible to obtain a small peak with a retention time the same as that of eugenol.

Identification of the other minor components of the Nigerian *Ocimum gratissimum* oil is in progress with a view to supplying further evidence for their chemotaxonomy along the lines suggested by Guenther (1958) and Gildemeister and Hoffmann (1961).

Aqueous solutions of the oil of *O. gratissimum* have been shown to have appreciable antibacterial activity (Table 3). However, it seems unlikely that the methods employed locally for the preparation of aqueous extracts (decoction) of this plant would permit retention of sufficient of the volatile material in the aqueous phase for it to have any anti-bacterial effect. Experiments tend to confirm this, since none of the extracts prepared were inhibitory to any of the enteric organisms used. Nevertheless, these extracts may be effective against diarrhoea by a direct action on the smooth muscle. This possibility is being looked in too.

During these investigations, the essential oil of *O. gratissimum* leaves was found to be active against a wide range of organisms – both Gram-positive and Gram-

negative. It was, however, not active against *Ps. aeruginosa* an organism which is known to be resistant to many anti-bacterial agents (Sykes, 1965).

Anti-bacterial agents are active only in the phase natural to the bacteria *i. e.* the aqueous phase. Thus, when drops of O. *gratissimum* oil are placed on the surface of a seeded agar plate, the active components of the oil must dissolve in the water surrounding the bacteria before it can act against them. A quantitative estimate of the activity of the oil was obtained by determining the activity of aqueous solutions of the oil against a range of different bacteria. In terms of per cent saturation, the activity of aqueous solutions of the oil was similar to that of aqueous solutions of thymol (Table 3). The relative sensitivity of the different organisms to aqueous solutions of O. *gratissimum* oil and thymol were also similar, indicating that it is the thymol in the oil which is principally responsible for its activity. The greater activity of the aqueous solution of thymol may be explained by the fact that in the volatile oil-water system, the thymol will be partitioned between the oil and the aqueous phase and consequently the aqueous phase will not be completely saturated with thymol. Dilutions of the aqueous phase made subsequent to the removal of the oil phase will contain less thymol than if the original solution had been saturated.

Acknowledgement

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Antiviral Therapy in AIDS
Clinical Pharmacological Properties and Therapeutic Experience to Date

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Contents

Summary

The rapid spread of human immunodeficiency virus (HIV) infections and the grim outcome of these infections have focused interest on the possibilities for medical intervention. The end-stage of these infections, acquired immune deficiency syndrome (AIDS), was first recognised in 1981, and the causative agent isolated in 1983. Already several antiviral

drugs have been investigated. One initially promising drug, suramin, was found to have a net harmful effect but another, zidovudine (azidothymidine) has been shown to prolong life in AIDS patients. The properties of these and several other antiviral drugs such as antimoniotungstate (HPA-23), foscarnet (phosphonoformate) ribavirin, dideoxynucleotides, and interferons, are reviewed. The role of immunomodulating modalities such as plasmapheresis, bone marrow transplantation, thymosin, interleukin-2, inosine pranobex (isoprinosine), and cyclosporin are also discussed.

None of the currently available drugs holds promise as monotherapy. Through analysis of the experience with these drugs and the increasing knowledge of HIV pathogenesis, new drugs can be designed. It seems increasingly clear that drugs will eventually have to be used in combination in order to reduce toxicity, exploit therapeutic synergy, and reduce the risk of HIV resistance. The theoretical and experimental background for such combinations are currently being elucidated.

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The underlying cause of the acquired immune deficiency syndrome (AIDS) has so far eluded treatment. The disease is associated with a selective depletion of T4 helper/inducer lymphocytes and concomitant complications of immunodeficiency such as opportunistic infections, Kaposi's sarcoma or neural damage (MMWR 1985). The aetiological agent of AIDS is an exogenous C-type retrovirus that has variously been called lymphadenopathy-associated virus (LAV), human T-cell lymphotropic virus type III (HTLV-III), or AIDS-associated virus (ARV) [Barre-Sinoussi et al. 1983; Levy et al. 1984; Popovic et al. 1984], but is now referred to as the human immunodeficiency virus (HIV) [Coffin et al. 1986].

The perception of HIV infection has been dominated by the end-stages of the disease, AIDS, as defined by the Centers for Disease Control for epidemiological purposes. Now that the causative virus has been identified, the disease can be viewed as a human viral infection with different complications related to hitherto undefined cofactors. Recently, increasing attention has focused on the neurotropic nature of the virus and its propensity to infect cells of the monocyte/macrophage lineage (Ho et al. 1985a, 1986).

The testing of serum samples for HIV-specific antibodies provides evidence of prior exposure to the virus. In the US alone, more than a million people are estimated to be infected with the virus and over 25,000 have been diagnosed as having AIDS (Barns 1986). However, HIV has spread into a pandemic with a particularly threatening situation in tropical Africa, where more than 15% of blood donors in certain areas have anti-HIV antibodies (Kreiss et al. 1986; Serwadda et al. 1985). A small portion of infected people may carry HIV virus in their blood in the absence of detectable serum antibody (Mayer et al. 1986; Salahuddin et al. 1984). Up to 24% of people who are seropositive for HIV may develop AIDS (Mathur-Waugh et al. 1985).

Several levels of intervention are envisioned for HIV infection:

1. Prevention of infection by epidemiological approaches and vaccination.
2. Treatment of complicating infections and neoplasms.
3. Inhibition of virus replication in the infected host.
4. Reconstitution of the defective immune response.

Approaches to the treatment of AIDS have paralleled our understanding of the disease. Initially, therapy was concentrated on various complications of the illness such as *Pneumocystis carinii* pneumonia or Kaposi's sarcoma. With further definition of the immunological defects, therapies were aimed at reconstituting the immune system. Then discovery of the causative agent, HIV, stimulated great interest in antiviral agents.

In this review we focus on two major approaches to control of the early stages of HIV infection as well as full-blown AIDS: firstly, specific

inhibition of HIV replication; and secondly, immunological reconstitution. In discussing the role of antiviral drugs and immunomodulation one should consider the possibility of early therapeutic intervention in asymptomatic carriers of HIV prior to the establishment of immunodeficiency or overt disease.

With increasing understanding of the infection of cells of the monocyte/macrophage lineages, quiescent infections, and virus spread to privileged areas such as the brain, models of antiviral activity on virus-producing cells become complex. However, it might prove possible to alter the virus-host balance such that the host can successfully deal with infected cells. Alternatively, it is possible that drug-induced reduction of biologically active virus products by the few infected cells might significantly alter the clinical course of the disease.

1. Antiviral Therapy

Human viral infections are difficult to control, but some success has been achieved through the application of vaccines in the eradication of smallpox and reduction of the incidence of diseases such as polio and measles. In addition, antiviral therapy has been developing and specific agents are now available for the treatment of particular infections: e.g. amantadine for influenza, and vidarabine and acyclovir for herpes simplex and varicella/zoster. In addition, interferon-α has demonstrated clinical antiviral activity against herpes simplex, varicella/zoster, cytomegalovirus, hepatitis B, laryngeal papillomatosis and respiratory infections (Hirsch & Kaplan 1985).

1.1 Possible Targets in HIV Replication

A number of molecular events in the retrovirus replication cycle are potential targets for selective inhibitors that cause minimal toxicity for the host cell (Lowy 1985) [see table I]:

1. Early steps in HIV infection include adsorption to a specific cellular receptor near or identical to the CD4 molecule (Dalgleish et al. 1984), penetration, and uncoating in the cytoplasm. Adsorption and penetration could be blocked by specific monoclonal antibodies and synthetic oligopeptides which are homologous to certain portions of the HIV envelope protein.

2. An important site for antiviral inhibitors is the HIV-specific reverse transcriptase enzyme that transcribes the viral genomic RNA into proviral DNA, which is subsequently integrated into host chromosomal DNA or remains as cytoplasmic plasmids (see section 1.2). The virus-specific RNase H, which normally degrades the viral genomic RNA during the transcription process into double-stranded proviral DNA, could be utilised to cleave atoxic oligonucleotide-like compounds into toxic products. If HIV-specific 'integrase' activity is coded for by the *pol* gene (which encodes the reverse transcriptase enzyme), integration of the HIV provirus into the host DNA might be inhibited.

3. Proviral DNA is expressed by transcription

Table I. Potential points of attack in the HIV replication cycle

Steps in viral replication	Possible intervention
Adsorption to CD4+ molecule	Receptor-blocking antibodies, oligopeptides
Entering cell	Membrane stabiliser: AL721
Uncoating	? Interferon
Reverse transcriptase	Inhibitors: suramin, antimoniotungstate (HPA-23), foscarnet (phosphonoformate), ?ansamycin Chain terminators: zidovudine (AZT), dideoxynucleosides
RNase H	Cleavage of atoxic prodrugs
Integration	?
Activation	Cyclosporin
Transcription	? *art* inhibitor, ? oligonucleotides
Translation	Ribavirin, ? *tat* inhibitor Cysteine substitution: D-penicillamine
Post-translational modification	? Inhibition of virus-specific protease or cleavage of atoxic prodrugs, ? glycosylation
Assembly	Interferons, ? suramin
Release of suppressive factors	? Vaccine
Cell-bound viral antigens	? Toxic monoclonal antibodies
Syncytia formation	HLA or CD4+ blocking agents

/ replication cycle

ible intervention

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brane stabiliser: AL721

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itors: suramin, noniotungstate (HPA-23), arnet (phosphonoformate), amycin

in terminators: zidovudine), dideoxynucleosides

vage of atoxic prodrugs

esperin

inhibitor, ? oligonucleotides

virin, ? *tat* inhibitor

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of the integrated proviral DNA sequences into viral messenger RNA, which is modified during post-transcriptional processing, prior to translation, into virus-specific proteins. The virus-encoded protease might function at this level and be utilised to cleave atoxic prodrugs into toxic compounds.

4. During maturation, viral envelope proteins are synthesised, glycosylated and inserted into the plasma membrane. Viral RNA is condensed and assembled with viral core proteins before virus particles are released by budding off the cell surface. Interferons could interfere with these processes.

5. HIV replication is regulated by unique types of genetic control called transcriptional transactivation and antirepression transactivation. The HIV *tat* and *art* genes' coding for the transacting factors that stimulate viral transcription and translation could be targets for antiviral therapy (Dayton et al. 1986; Sodroski et al. 1985, 1986). The *tat* gene codes for a transactivator protein which increases the rate of virus synthesis by regulating transcription and/or translation of mRNA into proteins. The *art* gene product acts after transcription to relieve regulation of viral RNA.

1.2 Inhibitors of Reverse Transcriptase

As discussed above, retroviruses contain a specific enzyme, reverse transcriptase, which is essential for virus replication. Selective inhibitors of reverse transcriptase and retroviral replication include template/primer binding compounds such as distamycin or diarylidones that interact with adenine-thymine base pairs, polyanionic substances such as suramin, pyrophosphate analogues such as foscarnet (trisodium phosphonoformate), and template analogues such as single-stranded polyribonucleotides and oligonucleotides (for a review, see Shannon 1984).

Inhibitors that bind to the enzyme include ansamycin (a rifampicin analogue) while chelating agents, such as thiosemicarbazones, 8-hydroxyquinolines and isoniazid, are active against the reverse transcriptases of many animal retroviruses.

Recently, most efforts have concentrated on nucleoside analogues, e.g. zidovudine (azidothymidine; AZT) and dideoxynucleotides, which have a 3′-chemical configuration that does not allow proviral DNA chain elongation when the reverse transcriptase binds the drug instead of the natural deoxynucleotide.

Selected properties of some of the drugs that are currently undergoing clinical trials are summarised in tables II and III.

1.2.1 Suramin

Suramin sodium is a hexasodium salt of naphthalenetrisulphonic acid. Originally, suramin was used in treating trypanosomiasis and onchocerciasis in tropical Africa. Subsequently, it was shown to inhibit the reverse transcriptase activities of such retroviruses as murine leukaemia and sarcoma viruses and avian myeloblastosis virus (De Clercq 1979). The drug interferes with many biological functions including arginine- and lysine-specific ester proteases, some RNA polymerases, and virus-mediated cell fusion (De Clercq 1982). It also decreases the binding of immune complexes to erythrocytes.

In reverse transcription, suramin is thought to interact with template and/or primer binding sites and can inhibit the enzyme by 50% in the range of 0.1 to 1.0 mg/L (Mitsuya et al. 1984). Suramin also inhibits the replication of HIV in the H9 human T-cell line and in T4+ lymphocytes. This inhibition occurs in the range of 50 to 1000 mg/L and

Table II. Dosage of drugs that have been or are being tested against HIV clinically

Drug	Elimination half-life	Route(s) of administration
Suramin	40 days	IV; IM
Antimonioturgstate (HPA-23)	20 min	Continuous or bolus IV; IM
Foscarnet (phosphonoformate)	1-3h	Continuous IV
Ribavirin	24-72h	Oral
Zidovudine (azidothymidine)	1h	Oral

Abbreviations: IV = intravenous; IM = intramuscular.

Table III. Attainable serum concentrations and *in vitro* inhibitory concentrations of drugs that have been or are being tested against HIV infections

Drug	*In vitro* inhibition[a]	C_{max}	Clinical dose
Suramin	100 mg/L	50-100 mg/L	1-1.5 g/week
Antimoniotungstate (HPA-23)	60 mg/L	?	?
Foscarnet (phosphonoformate)	300 μmol/L	300-450 μmol/L	20 mg/kg/day
Ribavirin	100 mg/L	2-10 mg/L	0.6-2.4 mg/day
Zidovudine (azidothymidine)	9 mg/L	5-10 mg/L	1-2 g/day

a Concentrations showing more than 90% inhibition of infection of susceptible cells.

Abbreviation: C_{max} = peak serum concentration.

probably reflects a decrease in reverse transcriptase activity. However, the high protein binding makes predictions from *in vitro* experiments difficult.

Clinical Pharmacological Properties

Plasma suramin concentrations of more than 100 mg/L are often achieved in the treatment of parasitic infections. In this setting suramin has considerable toxicity. Given as a bolus intravenous injection, suramin has a very long half-life (about 40 days), permitting intermittent dosage schedules. A study of its pharmacokinetic properties in 4 AIDS patients who were given doses of 6.2g over 6 weeks demonstrated that plasma concentrations reached 100 mg/L for several weeks, with a half-life of 44 to 54 days after the last dose. Approximately 99.7% was bound to plasma proteins. Urinary excretion accounted for the elimination of most of the drug (Collins et al. 1986).

Therapeutic Experience

Since suramin was already available for use in parasitic infections, it was able to be rapidly evaluated in patients with HIV infection. In a preliminary open uncontrolled trial, plasma concentrations of 100 mg/L were achieved in 10 patients with AIDS or AIDS-related complex (ARC). Adverse reactions such as transient skin eruptions, fevers, proteinaemia and liver function abnormalities were tolerable (Broder et al. 1985). Most side effects peaked during the second week and then subsided. Blood cultures from 4 patients were positive, but became negative during the course of therapy. Once suramin was withdrawn, virus-positive cultures reappeared. Despite the observed virustatic effect during treatment, there was no significant clinical or immunological improvement.

Similar findings were reported in a trial in 8 German homosexual men who were given 6.2g over 6 weeks followed by maintenance doses of 1 g/week (Busch et al. 1985). A single African individual tolerated suramin better than the other patients, as had been observed in an earlier study of 5 AIDS patients from Rwanda who were given 20 mg/kg every 5 days for 35 days. These patients only experienced transient fever and weakness (Rouvroy et al. 1985).

In a recently terminated multicentre trial involving 7 US institutions, data presented by Cheson et al. (1986) indicated that the virus could be isolated from several patients maintained on 0.5 g/week (in whom suramin serum concentrations were below 100 mg/L), and that higher doses were required to interfere with the isolation of HIV. No clinical benefit was reported (Levine et al. 1986).

Adverse Effects

Suramin plasma concentrations of 100 mg/L or greater can suppress T-cell growth but also cause toxicity *in vivo*, resulting in renal damage, fever, photosensitivity and skin eruptions. Although higher concentrations obtained by administration of 1 to 1.5 g/week resulted in lower virus isolation rates, the side effects, including adrenal insufficiency, were severe. It was concluded that the net effect of suramin was harmful in the patients tested.

Suramin is no longer being considered as a single-drug treatment modality (Levine et al. 1986).

1.2.2 Antimoniotungstate (HPA-23)

Initially described as ammonium 5-tungsto-2-antimoniate (TA), later studies indicated that antimoniotungstate is a mineral-condensed heteropolyanion (HPA) with the formula ammonium 21-tungsto-9-antimoniate (MW 6800) [Fisher et al.

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1976]. It was first shown to inhibit mouse leukaemia-sarcoma virus in 1971, and later to reduce the development of disease caused by Friend leukaemia and Moloney murine sarcoma virus (Jasmin et al. 1974).

Antimoniotungstate is a competitive inhibitor of reverse transcriptase activities of murine and human retroviruses. HIV reverse transcriptase activity is completely inhibited by concentrations of 60 mg/L (Dormont et al. 1985). However, the drug has little effect on the replication of HIV *in vitro* (Balzarini et al. 1986).

Clinical Pharmacological Properties

The elimination half-life of antimoniotungstate after bolus intravenous injection is less than 20 minutes. In French studies, the drug has been administered in repeated doses of 50 to 200 mg/day by slow intravenous injection or infusion on 5 days a week for several months.

Therapeutic Experience

Results have been reported from a preliminary trial involving 4 patients with AIDS or AIDS-related complex (Rozenbaum et al. 1985). Although no virus reverse transcriptase activity could be measured in virus cultures during treatment, such activity was detected in 2 of 4 patients 30 days following the termination of treatment. No significant effect on either T-cell subpopulation was seen.

Many patients have now been treated with antimoniotungstate in France using different dosage schedules, but at present only anecdotal data are available. Information on a limited number of additional patients enrolled in open studies in France were presented in the International Conference on AIDS in Paris, June, 1986. The authors' impressions did not differ from those of the original report. Several centres in the US are now evaluating antimoniotungstate under phase I protocols.

Adverse Effects

During the clinical trials discussed above, platelet counts decreased and hepatic transaminases were elevated, but these returned to normal values after the drug was discontinued.

1.2.3 Foscarnet (Phosphonoformate; PFA)

Foscarnet is the trisodium salt of phosphonoformic acid (phosphonoformate). It was first shown to be a virus inhibitor in 1978 (Helgstrand et al. 1978). Like phosphonoacetic acid (PAA), it is active against herpes simplex virus, cytomegalovirus and a number of animal retroviruses including the visna lentivirus (Sundquist & Larner 1978). Foscarnet, a pyrophosphate analogue, is a non-competitive inhibitor of reverse transcriptases (Sundquist & Öberg 1979). In HIV-infected H9 cells, a concentration of 100 μmol/L inhibited virus replication by 98%, as measured by reverse transcriptase activity, without concomitant cell toxicity. A concentration of 680 μmol/L completely inhibited virus replication, even if added 4 days after infection, but some suppression of cell growth did occur at that concentration. The reverse transcriptase activity associated with HIV particles is extremely sensitive and is completely abolished by 5 μmol/L foscarnet (Sandström et al. 1985; Sarin et al. 1985a). T-Cell colony counts increased in cultures from patients with AIDS when foscarnet was added to the medium (Beldekas et al. 1985).

Clinical Pharmacological Properties

The elimination half-life of foscarnet in animals is 1 to 3 hours after subcutaneous or intravenous injection. About 30% of the dose accumulates in bone and the remainder is excreted unaltered in the urine. No effect on calcium metabolism or the bone marrow has been seen. Clearance of the drug from bone is biphasic in animals with a primary phase half-life of 8 days and a subsequent phase half-life of about 1.5 years. There are case reports indicating that foscarnet can pass through the blood-brain barrier (B. Öberg, personal communication).

Therapeutic Experience

Two series of patients were reported at the International Conference on AIDS in Paris, 1986. Farthing (London) presented data on 11 AIDS/AIDS-related complex (ARC) patients given con-

tinuous infusions of 20 mg/kg foscarnet daily for 3 weeks: 5 patients reported mild headaches, 2 reversible anaemia and 3 reversible rise in serum creatinine. Viral cultures became negative in 6 patients for the duration of the treatment, while cultures remained positive or showed a variable response in the remaining 5. The virus was regularly isolated from 4 untreated matched controls. Using a similar protocol, Bergdahl (Stockholm) presented data on 14 AIDS/ARC virus-positive patients. In this study few side effects were observed. Of the duplicate cultures obtained prior to treatment, 20% were negative compared with 62% of those obtained during treatment and 36% of those after treatment. In both studies a reduction of symptoms was reported while on the drug.

Adverse Effects

More than 140 immunocompromised transplant patients have been treated with foscarnet for complicating cytomegalovirus infections. In these patients, serum concentrations of 300 to 450 μmol/L caused minimal toxicity. In cytomegalovirus-infected transplant patients a fall in haemoglobin, a rise in serum creatinine and, in some instances, increased levels of serum calcium have been observed. Although these observations might relate to the underlying disease, an effect of foscarnet cannot be excluded. One patient who was given 10 times the recommended dose showed acute toxicity consisting of reversible hallucinations and flapping tremor.

1.2.4 Zidovudine (Azidothymidine; AZT)

Zidovudine [3′-azido-3′deoxythymidine (AZT)] has also been called 'compound S' or BW A509U. In 1974, it was discovered that zidovudine interfered with the release of C-type retrovirus in cell cultures infected with Friend virus without affecting the increase of intracisternal A-type particles (Krieg et al. 1978; Ostertag et al. 1974). Its synthesis was described in 1978 by Lin and Prusoff. The unphosphorylated form of the drug is inactive, but becomes a competitive inhibitor of reverse transcriptase activity after conversion to a triphosphate by cellular kinases. Zidovudine appears to act as a chain terminator because of replacement of the 3′-OH group with an azido (N_3) group. HIV reverse transcriptase is approximately 100 times more sensitive to zidovudine inhibition than cellular DNA polymerases (Furman et al. 1986). Antiviral effects have been demonstrated *in vitro* using concentrations of 1 to 10 μmol/L to protect T-cells from HIV infection (Mitsuya et al. 1985). This effect is reversed in a dose-dependent manner by thymidine. At a concentration of 10 μmol/L, zidovudine has only a marginal effect on antigen or mitogen activation, immunoglobulin production and cell viability of OKT4+ T-cells peripheral blood leucocytes. Zidovudine triphosphatase has high affinity for HIV reverse transcriptase (K_i = 0.0022 μmol/L) compared with the physiological nucleoside thymidine triphosphate (K_i = 1.7 μmol/L) [Vrang et al., Svenska Läkarsällskapets Riks-tämma, Stockholm, 1986].

Clinical Pharmacological Properties

In a recent phase 1 trial, zidovudine was administered intravenously in a dose of 1 to 2.5 mg/kg every 8 hours or 2.5 to 5mg every 4 hours. A single 1-hour intravenous dose of 2.5 mg/kg gave a peak concentration of approximately 5 μmol/L, with an elimination half-life of about 1 hour. An oral dose of 5 mg/kg gave approximately the same peak concentration and half-life, with a calculated bioavailability of about 60%. Four hours after the start of an infusion of 5 mg/kg, a concentration of 0.86 μmol/L was measured in the spinal fluid of 1 patient with a plasma concentration of 1.14 μmol/L (Klecker et al. 1987; Yarchoan et al. 1986).

Therapeutic Experience

19 patients with AIDS or ARC have completed a phase I trial (Yarchoan et al. 1986) evaluating intravenous doses ranging from 3 to 30 mg/kg/day for 2 weeks followed by a corresponding oral dose of 6 to 60 mg/kg/day for 4 weeks. The virus could be detected sporadically with a trend favouring inhibition at higher doses. T-helper cells, T4/T8 ratios, and delayed hypersensitivity were increased during therapy. Two patients with fungal nailbed infections and 1 with aphthous stomatitis im-

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Because of the initially promising results, a multicentre phase II controlled clinical trial of zidovudine at an initial oral dose of 250mg 6 times daily was commenced in the US. This study was terminated prematurely because an independent review board found a significant effect on opportunistic infections and decreased mortality in the group treated with zidovudine. This double-blind trial included 282 adults in 12 centres (85 AIDS and 60 ARC patients received zidovudine while 75 AIDS and 62 ARC patients were given placebo). The AIDS patients were eligible only if they had had an initial episode of *Pneumocystis carinii* pneumonia within 120 days; the trial did not include patients with Kaposi's sarcoma. Only 1 patient died in the zidovudine group compared with 19 deaths in the placebo group. Patients taking zidovudine had fewer opportunistic infections and gained more weight than those on placebo. Zidovudine is now being marketed in many countries throughout the world.

Adverse Effects

Two patients were withdrawn from the phase I study (Yarchoan et al. 1986) due to progressive Kaposi's sarcoma and a possible drug reaction, respectively. Nine subjects complained of mild headaches, and decrease in haematocrit that was not dose-related was observed in several patients (1 developed pernicious anaemia). Of the 4 patients on the highest dose, 3 experienced decreases in either T-helper cells or total lymphocytes.

About one-quarter of all patients in the phase II study developed severe megaloblastic anaemia due to bone marrow depression. 27% of the patients on zidovudine required at least 1 blood transfusion compared with 8% of those who received placebo. It is possible that thymidine substitution might be able to counter this side effect (Broder 1986). The magnitude of this problem might be so great that zidovudine cannot be used for long term monotherapy.

1.2.5 2′,3′-Dideoxynucleosides

Several 2′,3′-dideoxynucleosides have demonstrated inhibitory effects on murine retroviruses in mammalian cell lines. These derivatives must be phosphorylated by the cell kinase and act as DNA chain terminators like zidovudine (Mitsuya et al. 1987a). In a recent study, 2′,3′-deoxyadenosine, -guanosine, -inosine and -cytidine (ddCyd) inhibited HTLV-III_B replication in ATH-8 T-cells *in vitro* without affecting cell viability. Concentrations of these compounds 10 to 20 times those required to inhibit HIV left antigen- or lectin-driven proliferation intact in a 3-day assay (Mitsuya & Broder 1986).

Most attention has focused on 2′,3′-dideoxycytidine. It is phosphorylated equally well by infected as by uninfected ATH-8 cells. The inhibition is reversed by the physiological nucleoside deoxycytidine. Its uptake is at least partly dependent on a nucleoside carrier (Cooney et al. 1986). Phase I trials are now underway at the National Cancer Institute in the US.

1.2.6 Ansamycin (Rifabutine)

Ansamycin was synthesised as a derivative of rifamycin S. It is active against *Mycobacterium avium-intracellulare* and is currently undergoing clinical trials against this infection in AIDS patients.

In concentrations of 0.1 to 0.8 mg/L, ansamycin inhibits HIV replication *in vitro*. Its mechanism of action is thought to be inhibition of the DNA-dependent RNA transcriptase in Gram-positive bacteria and some eukaryotic cells and viruses against which it is active (Arora 1983). HIV replication in human peripheral blood leucocytes *in vitro* is inhibited, presumably by ansamycin binding to the reverse transcriptase (Anand et al. 1986).

Plasma concentrations of 0.2 to 0.5 mg/L, which persist for 24 hours, are achieved following administration of doses of 75 to 300mg ansamycin. These concentrations have been stated to be non-toxic *in vivo* (Coulaud 1986). Early phase I clinical trials with ansamycin are now underway.

1.3 Other Potential Anti-HIV Drugs

1.3.1 Interferons

Interferons (IFNs) are natural proteins produced during the course of viral infection, or subsequent to challenge by other natural or synthetic substrates such as double-stranded RNA. They have a broad spectrum of antiviral activity against DNA and RNA viruses. There are three major types of interferons: *alpha, beta* and *gamma.* Human interferon-α (HuIFNα) is induced from virus-infected leucocytes and exists in 14 subtypes. Interferon-β (HuIFNβ) produced by fibroblasts has two forms, but there is only one form of immune interferon-γ (HuIFNγ) which is produced by T-cells. Receptors for interferon-γ are distinct from those for interferon-α or interferon-β (for a review, see Hirsch & Kaplan 1985).

Leucocyte interferons have been used for the prophylaxis and therapy of many types of virus infections. They have been found to reduce the incidence and symptoms of rhinovirus infections, to suppress varicella/zoster infections in immunocompromised children with cancer, and to reduce cytomegalovirus reactivation in renal transplant patients. Due to the production of interferon-α and interferon-γ by recombinant DNA technology, availability is now adequate for large-scale clinical trials to be carried out.

All interferons appear to act indirectly by binding to specific cell surface receptors and inducing the production of cellular enzymes which are responsible for the antiviral activity. Specific antiviral mechanisms vary from one virus type to another and include inhibition of transcription, translation, assembly, or release of the virus. Numerous animal retroviruses are sensitive to the action of interferons both *in vitro* and *in vivo*, especially those of murine, feline and primate origin. In mouse model systems, assembly and subsequent release of viral particles seems to be a major site of action, so that virus particles accumulate at the cell surface (Aboud & Hassan 1983).

Recently it has been shown that recombinant interferon-α-A (rIFN-alpha-A), inhibits the replication of HIV in human peripheral blood leucocytes *in vitro*. When cultures were treated with recombinant interferon-α-A (4 to 64 U/ml) 24 hours prior to virus challenge, significant reductions in virus yield, reverse transcriptase activity and expression of viral antigens were observed (Ho et al. 1985b).

Therapeutic Experience

In patients with, or at high risk from, AIDS, low levels of the normal acid-stable interferon-α are found, while there is an increase in an acid-labile variant (Eyster et al. 1983). Interferon-α purified from leucocytes (Cantell) or recombinant interferons of different subtypes have been used in the treatment of Kaposi's sarcoma in AIDS (for a review, see Lotze 1985). Interferons have been administered using many different protocols ranging in dosages from 3 to 55 million units intramuscularly or intravenously daily to 3 times per week for 20 to 60 days. Complete or partial responses of Kaposi's sarcoma lesions have been noted in 25% and 50%, respectively, of patients treated with higher doses. The natural course of Kaposi's sarcoma in this setting, however, has not been evaluated. The mechanism of action is compatible with the antiproliferative effect of interferons, which is supported by the high doses necessary for clinical effect. Interferon-α seems to be equally effective as chemotherapy against Kaposi's sarcoma in AIDS patients, but with fewer complicating opportunistic infections (Real et al. 1986). However, there has been little evidence of improvement in immune parameters.

Low levels of interferon-γ are found in patients at risk of or with AIDS (Murray et al. 1984). Also, natural killer cells are often defective and addition of interferon-γ *in vitro* can correct this deficiency to some degree. Interferon-γ can also stimulate B-cell maturation (Sidman et al. 1984). However, clinical trials have generally not demonstrated any clinical benefit or change in immune parameters by treatment with interferon-γ.

The available studies of interferons are difficult to evaluate since investigators have used different interferon preparations, different dosages and dosage schedules, different patient selection criteria,

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Adverse Effects

The side effects of high doses of interferon-α are clinically similar to AIDS-related complex, including fever, chills, myalgia, effects on the CNS (including extreme fatigue) and leucopenia. These symptoms are frequently dose-limiting, although there is a clinical impression that HIV-infected patients tolerate higher doses than other patients.

1.3.2 Ribavirin

Ribavirin is a nucleoside consisting of D-ribose attached to a 1,2,4-triazole carboxamide. Synthesised in 1972, ribavirin was found to be active against a number of RNA and DNA viruses, including influenza A and B, respiratory syncytial virus, measles, herpes simplex and varicella/zoster (Chang & Heel 1981; Witkowski et al. 1972).

Topical administration of a small-particle ribavirin aerosol has provided promising results in influenza and respiratory syncytial virus infections. Ribavirin has also been of some benefit in the treatment of Lassa fever. The mechanism of its antiviral effect is poorly understood and probably not the same for all viruses. In 1977 it was found to inhibit murine retrovirus replication *in vitro* and *in vivo* (Shannon 1977). Its mechanism of action is thought to involve alterations of the intracellular guanosine pool and the guanylation step required for 5' capping of viral messenger RNA. Ribavirin has been found to suppress HIV replication in continuous cell lines and human peripheral blood leucocytes. Exposure of cultures to doses of 50 to 100 mg/L for periods of 8 to 9 days inhibited reverse transcriptase activity and HIV immunofluorescence. If additional drug was added after 5 days, virus expression was further delayed but not prevented (McCormick et al. 1984).

Clinical Pharmacological Properties

Ribavirin can be administered orally and is slowly eliminated via the kidneys with an elimination half-life of about 72 hours. A considerable amount of drug is retained in red blood cells and other tissues. In cancer trials, more than 1000 patients have received doses of 400 to 800 mg/day for 10 days or 1000 mg/day for 5 days with few adverse reactions being noted. Plasma concentrations have been maintained at 6 to 15 mg/L in AIDS and ARC patients. Concentrations of ribavirin in the CSF of 3 treated AIDS patients were 67 to 115% of those found in the plasma (Crumpacker et al. 1986).

Therapeutic Experience

Preliminary findings from a phase I study were reported by Crumpacker et al. (1986). In this study ribavirin was given orally to 9 AIDS or ARC patients. Virus cultures became negative in 2 patients during treatment, and there was an increase in ConA stimulation, T4 cells, and improved clinical signs. Two patients required blood transfusion. Double-blind placebo-controlled trials are now underway in patients with AIDS-related complex.

Adverse Effects

The primary toxicity of ribavirin has been a reversible inhibition of haemoglobin synthesis.

1.3.3 Other Antiviral Drugs

Several of the abovementioned drugs are already being modified, i.e. suramin (Balzarini et al. 1986) and foscarnet (Vrang & Öberg 1986). A number of DNA chain terminators analogous to zidovudine that utilise the 'unfaithfulness' of the HIV reverse transcriptase are being synthesised and tested in order to find drugs with an increased therapeutic index (Mitsuya et al. 1987a).

The cysteine analogues D- and L-penicillamine have been investigated due to their affinity for proteins with high cysteine content such as the HIV nucleotide-binding protein. A D-penicillamine concentration of 40 mg/L was required to totally inhibit HIV infection of H9 cells, while concentrations above 100 mg/L had no cellular toxicity (Chandra & Surin 1986).

Oligonucleotides complementary to sequences

close to the $tRNA^{Lys}$ primer binding site or at the mRNA splicing donor or acceptor sites have also been found to inhibit HIV *in vitro* (Zamecnik et al. 1986).

Analogous to the toxic effect of monoclonal-ricin A conjugated anti-interleukin-2 receptor antibodies against HTLV-I infected cells *in vitro*, drug-conjugated antibodies might be directed against HIV-infected cells expressing, for example, gp41 or gp120 (Krönke et al. 1986). The HIV RNase H or HIV-specific protease might be utilised to cleave atoxic prodrugs into cytotoxic intracellular drugs.

Israeli investigators have used a liquid compound, AL721, in an attempt to affect the virus adsorption step. AL721, which reduces cholesterol levels in peripheral blood leucocyte membranes, has been found to inhibit HIV infection of the H9 cell line and human peripheral blood leucocyte *in vitro*. Apparently, AL721 causes no side effects or toxicity *in vivo* (Sarin et al. 1985b).

Brief exposure of HIV to a non-ionic surfactant spermicide, nonoxygenol-9, has been found to prevent infection of H9 cells *in vitro* and might prove valuable for local use to reduce viral transmission by the sexual route (Hicks et al. 1985; Voeller 1986).

1.4 Combination Therapy

Combinations of antiviral agents that act by different mechanisms at various sites may reduce toxicity by lowering the required serum concentration of an individual drug. Recent findings indicate that a number of agents have a true synergistic effect: both foscarnet and zidovudine with interferon-α (Hartshorn et al. 1986a,b), ribavirin with foscarnet (Vogt & Hirsch 1986), both suramin and acyclovir with zidovudine, as well as combinations of different dideoxynucleosides (Mitsuya et al. 1987a). This offers one of the more promising approaches to the design of future therapeutic regimens where synergistic antiviral effects of various drugs might allow administration of non-toxic doses of each of the combined drugs.

The propensity for HIV to undergo rapid genetic modification, and thus quickly select for resistance, might make this treatment design even more important. Drugs with different modes of action (see section 1.1) would then be preferred; for example, interferon plus reverse transcriptase inhibitors such as foscarnet or zidovudine. In herpes simplex infections it has been found that polymerase resistance to the chain terminator acyclovir does not affect sensitivity to foscarnet (Larder & Darby 1986). However, the finding that HIV is neurotropic will limit the use of certain antiviral agents unless they pass the blood-brain barrier in sufficient concentrations to affect the HIV reservoir in the central nervous system.

2. Immunomodulating Therapies

Various strategies have been developed to correct the *in vivo* immunodeficiency caused by HIV infection. It is possible that antiviral drugs may be successful only if used in combination with immunotherapy.

2.1 Plasmapheresis

Circulating immune complexes, antilymphocyte antibodies and suppressor factors of allogeneic lymphocyte proliferation have been detected in patients with AIDS and AIDS-related complex (Forwell et al. 1986; Kloster et al. 1984). One approach towards immune reconstitution could be the removal of such substances by plasmapheresis. Cats infected with feline leukaemia retrovirus could be cleared of the virus by extracorporeal immunoadsorption on Staphylococcus protein-A columns in the presence of high levels of anti-gp70 antibodies (Snyder et al. 1984).

2.1.1 Therapeutic Experience

In limited trials, plasmapheresis alone has not benefited AIDS patients. If plasma was adsorbed on protein-A columns, both immune complexes and antilymphocyte antibodies, but not suppressor factors, were removed. In some patients, the number of Kaposi's sarcoma lesions was reduced, but there was no net effect on survival. An increase in T-helper cells was also observed.

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phapheresis led to clinical improvement in patients with polyneuropathy and antimyelin antibodies. Decreased levels of immune complexes, antilymphocyte antibodies and suppressor factors were observed. In contrast to other procedures, there was a slower return of immune complexes and antilymphocyte antibodies, while suppressor factors returned at the same rate as after plasmapheresis (about 3 weeks) [Kiprov et al. 1986].

2.1.2 Adverse Effects

Adsorption over protein-A columns has been associated with transient fever and chills. Occasionally patients have experienced type I reactions in conjunction with apheresis over protein-A columns, which could be due to the release of minute amounts of protein-A from certain columns or to the use of ethylene oxide for sterilisation of the plastic tubing.

2.2 Thymosin

Low levels of T4+ cells are consistently found in advanced stages of HIV infection. In most patients with AIDS there is a thymic atrophy, similar to that found in cats with immunodeficiency caused by feline leukaemia retrovirus (Elie et al. 1983; Essex et al. 1975; Grody et al. 1985). Therefore, restoration of immune function might be achieved through the administration of T-cell growth factors or agents that stimulate differentiation.

Thymosins are lymphokines found in the circulation that may be involved in the regulation of haematopoiesis, and may stimulate interleukin-2 production (Zatz et al. 1985). Substances that react as thymosin-α_1 in radioimmunoassays, but are undetectable by high performance liquid chromatography (HPLC), are found in the serum of AIDS patients (Goldstein et al. 1985). The nature of this immunologically cross-reactive material has not been determined.

Recently, immunological cross-reactivity and partial molecular homology between HIV *gag* protein p17 and thymosin-α_1 has been reported. Antisera against thymosin-α_1 were shown to have an antiviral effect (Sarin et al. 1986).

Several preparations of mixtures of thymic peptides are now available, such as thymosin fraction 5 (TF5), thymostimulin (TP-1), thymic humoral factor (THF), facteur thymique serique (TFX), or thymulin (FTS). Experience has been most extensive with TF5, a mixture of approximately 30 different low molecular weight peptides of which thymosin-α_1 (28 amino acids) is best characterised, and available in synthetic form (Goldstein et al. 1977). In addition, a biologically active pentapeptide fragment of thymopoietin, TP-5, is now under evaluation. However, different thymic peptides seem to have different biological properties and results generated with one preparation should not be generalised.

Treatment regimens in small series of patients have varied from injections of 30 to 120mg daily of TF5 to 50mg 3 times per week of TP-5. Only marginal improvements have been observed in mixed lymphocyte reaction (MLR) and mitogen-induced interleukin-2 production. Side effects have been limited to local pain and swelling over the subcutaneous injection sites (Lotze 1985).

2.3 Interleukin-2 (IL-2)

Interleukin-2 is a T-cell stimulating lymphokine, produced by T4+ and T8+ lymphocytes, that is induced by antigens in the presence of antigen-presenting cells or by mitogens if supplemented by interleukin-1 or phorbol myristic acid (PMA). It is a glycoprotein with an estimated molecular weight between 13 and 15kD. Interleukin-2 has a similar structure and function in different animals, although its degree of glycosylation exhibits interspecies variation.

Interleukin-2 was originally identified as a lymphokine necessary to propogate normal lymphocytes *in vitro*, and called T-cell growth factor (TCGF) [for a review, see Kolitz et al. 1985]. It is necessary for the growth and differentiation of peripheral blood leucocytes. Until recently, interleukin-2 was purified from mitogen-stimulated continuous cell lines but it has now been success-

fully cloned in *E. coli*. This non-glycosylated material has been purified and used in clinical trials. Although virtually free from extraneous proteins, preparations may contain traces of sodium dodecyl sulphate, a non-ionic detergent.

Interleukin-2 induces proliferation and differentiation of cells that express interleukin-2 receptors (Tac antigen). In addition, there is evidence for a second class of low affinity receptors. In the process of lymphocyte activation, specific receptors are expressed on T4+, T8+ and B-cells (Waldman et al. 1984). Interleukin-2 can also induce its own receptors, whereas antibodies against the receptor rapidly remove them.

Low concentrations of interleukin-2 have been found in serum from patients with AIDS. Their T-cells have an impaired ability to produce and respond to interleukin-2. Sera from AIDS patients also contain factors that inhibit interleukin-2-induced protein production in interleukin-2-dependent cell lines (Donnelly et al. 1986).

2.3.1 Clinical Pharmacological Properties

Interleukin-2 is eliminated via the kidneys. Following intravenous injection, its disappearance from the serum is biphasic, the half-lives of the two phases being 5 to 7 minutes and 30 to 120 minutes. Heat-labile inhibitors are found in the serum (Lotze et al. 1985; Siegel et al. 1985).

2.3.2 Therapeutic Experience

Both natural and recombinant interleukin-2 have been administered to patients in attempts to increase the number and function of lymphocytes. Doses of 250 to 1,500,000 units/day of natural or recombinant interleukin-2 have been administered by bolus or continuous intravenous infusion. To date, only minor improvements in immune parameters have been observed (Ernst et al. 1986). Although interleukin-2 may be intimately involved in the pathogenesis of AIDS, and might prove to be an essential adjuvant to antiviral therapy, several problems exist with its use as a therapeutic agent. It is probably present in localised high concentrations due to the close contact between producer and recipient cells. Various cell populations respond to different dose ranges. In contrast, high doses of intravenously administered interleukin-2 affect all cell populations and are rapidly cleared by the kidneys and by serum inhibitory factors. It is possible that latent proviruses can be activated by interleukin-2.

2.3.3 Adverse Effects

Some patients have experienced fever, chills, malaise, anorexia and weight gain in association with the administration of interleukin-2 (Lotze et al. 1985). Stimulation of lymphocytic disorders and skin rash have been seen in individual patients in conjunction with therapy. The maximum tolerable dose seems to be between 1 and 10 million units/day.

2.4 Inosine Pranobex (Isoprinosine)

Inosine pranobex is the *p*-acetamidobenzoic salt of *N,N*-dimethylamino-2-propanol and inosine in a 3 : 1 molar ratio. In early studies inosine pranobex was found to have weak antiviral activity. Recently, it has been shown that the drug partially inhibits HIV at concentrations of 200 mg/L (Pompidou et al. 1985). However, its potential immunostimulatory function has been of more interest. In animal models inosine pranobex has been shown to increase natural killer cell cytotoxicity, restore interleukin-2 production, and augment the antitumour activity of interferon in animal models (for a review, see Campoli-Richards et al. 1986).

Inosine pranobex has also increased mitogen-induced blastogenesis in peripheral blood leucocytes from patients with AIDS or lymphadenopathy syndrome (LAS), and stimulated *in vitro* interleukin-2 production in peripheral blood leucocytes from AIDS patients (Tsang et al. 1984).

2.4.1 Clinical Pharmacological Properties

The elimination half-life of the inosine moiety is 50 minutes following an oral dose and the major excretion product is uric acid. The other components are oxidised or glucuronidised and excreted. Inosine pranobex is generally well tolerated, although uric acid elevation is a concern.

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2.4.2 Therapeutic Experience

Inosine pranobex has been studied in a placebo-controlled double-blind trial in patients at risk from AIDS in doses of 1 or 3 g/day for 28 days. An augmentation was noted in natural killer cell activity as well as the total number of T-cells, and T-helper cells (Wallace & Bekesi 1986). In a recent limited trial, the drug was found to significantly reduce cytomegalovirus shedding in the semen of HIV-seropositive men (Drew et al. 1986).

Placebo-controlled double-blind trials have been carried out (but not yet reported) at 5 different US centres. A 6-month placebo-controlled double-blind trial utilising a dosage of 3 g/day and encompassing 960 Swedish and Danish HIV-seropositive men has also been initiated to determine the drug's clinical efficacy.

2.4.3 Adverse Effects

No serious adverse effects of inosine pranobex have been observed. Since inosine is broken down to uric acid, gout or renal dysfunction are relative contraindications.

2.5 Bone Marrow Transplantation

Immunological reconstitution has also been attempted with bone marrow transplantation or adoptive transfer of lymphocytes. This approach may be of potential benefit in the presence of effective anti-HIV therapy. Either autologous transplants could be purged of virus-containing cells, or allogeneic transfers carried out from uninfected donors. The transplants would have to be protected from infection by virus in the recipient through therapy with antiviral agents or neutralising antibodies. HLA matching must also be performed to avoid graft *versus* host reactions. These procedures might repopulate the blood with lymphocytes, but a virus reservoir in the central nervous system would not be affected.

At least 4 identical twins have undergone bone marrow transplantation, one under a protocol designed to eradicate virus-infected T-cells by vinblastine and total body irradiation. Transient rises in T4+ cells have been noted, but no definite clinical improvement (Lane et al. 1985).

One patient who received repeated lymphocyte transfers (10 to 20 billion/month), and a bone marrow transplant from his healthy identical twin, demonstrated a prolonged rise in T4+ and T8+ cells after the transplant. Maculopapular skin rashes and fever were temporarily related to the lymphocyte transfusions. In spite of immunological improvement, the patient continued to deteriorate (Lane et al. 1984). Of 15 patients who received cultured thymus cell implants, 7 showed increased responses to phytohaemagglutinin and mixed lymphocyte reaction. This was associated with a T-cell increase confined to the T8+ population (Lotze 1985). However, based on a series of 6 AIDS/ARC patients, it was concluded that thymic implants at present have no therapeutic value (Danner et al. 1986). The implants might have been too small, rejection might have destroyed the tissue, or the procedure might only have created an opportunity for further virus replication.

More recently, adoptive transfers of lymphocytes and bone marrow transplants have been performed in 3 identical twins in conjunction with suramin treatment (C. Lane, personal communication).

2.6 Cyclosporin

Working on the hypothesis that autoimmunity or activation of infected cells is a dominant trait of progression to AIDS, French investigators have given cyclosporin to patients with AIDS and ARC. Cyclosporin is a T-helper, cell-specific cytostatic drug used in kidney transplantation and experimentally in autoimmune diseases.

2.5.1 Therapeutic Experience

An initial study claimed significant short term improvement with cyclosporin in AIDS patients. Subsequently, 13 courses were given to 11 patients for 7 to 10 days starting at 4 mg/day until plasma concentrations of 100 to 200 nmol/L were maintained. The virus was isolated in 6 of 7 patients on days 0, 11, 18 and 40 and no significant alterations

in immunological parameters were noted on day 8.

2.5.2 Adverse Effects

About 20% of kidney transplant patients experience side effects with cyclosporin such as tremor, gastrointestinal symptoms, decreased appetite, increased hair growth and gingival swelling. There were also early reports of an increased incidence of lymphomas, but currently the major concern is the potentially serious problem of nephrotoxicity.

2.7 Vaccines

Although vaccines are not usually classified as therapeutic agents, an immunological response to certain subviral components or viral products might be manipulated to therapeutic advantage. Since HIV and some of its subgenomic components have been cloned, peptides expressed from selected clones could act as immunogens.

Factors that are directly immunosuppressive have been identified in other retroviral infections (Copelan et al. 1983). In feline leukaemia, the transmembrane protein p15E is immunosuppressive. A soluble suppressor factor that suppresses *in vitro* blastogenesis induced by mitogens is detected in the serum of AIDS patients (Laurence et al. 1983).

Virus-producing cells express viral antigens, particularly envelope proteins, on their surface. In animal models, the host-immune surveillance is able to pick out and destroy such cells (De Noronha et al. 1978; Enjuanes et al. 1979; Snyder et al. 1983). Virus envelope proteins (gp 120) are shed from infected cells and attach to their receptors on the T4 molecule. They could then interfere with the normal T-cell macrophage interaction (Lane et al. 1985; Sandström et al. 1986). This form of immunosuppression might be blocked by excess circulating anti-envelope antibodies.

Antibodies to such factors may be induced during early stages of HIV infection when the host immune system is still functional.

2.8 Other Agents

Analogous to the reasoning behind the use of cyclosporin is the proposed administration of anti-CD4 antibodies (Singer & Shearer 1986).

It has been suggested that diethyldithiocarbamate (DDTC) might inhibit HIV replication and be of benefit in AIDS patients (Pompidou et al. 1985), while indomethacin has been claimed to restore interleukin-2 and interferon-γ responses of peripheral blood leucocytes from AIDS patients to PHA (Palladino & Welte 1984).

Topical application of dinitrochlorobenzene (DNCB) has been claimed to enhance the immune response in AIDS patients (Mills 1986).

3. Conclusions: The Future of Antiviral Therapy in AIDS

3.1 Selection of Drugs

A multitude of drugs will soon require evaluation. Some of the desirable properties of such drugs are summarised in table IV. *In vitro* assay systems must be developed so that rational selection of potential antiviral compounds can be made. Fundamental aspects of these assays have not been defined, but substantial steps have been taken in that direction (Mitsuya et al. 1987b). Drugs may be introduced prior to infection, added during the time of infection, and not replenished or adjusted to a given concentration when the cells are fed. Viruses of one or more strains could be introduced at various multiplicities of infection or in cell-bound form,

Table IV. Desirable properties for an anti-HIV drug

1. Virustatic or cytotoxic for infected cells at concentrations that can be used *in vivo*
2. Low toxicity in long term studies
3. Minimal inhibitory effect on the immune system
4. Penetration into CNS
5. Synergistic with other anti-HIV drugs
6. Relatively long half-life
7. Adsorbed orally
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Future of Antiviral

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with or without adjuvant substances, e.g. polybrene. Host cells of different origins could be kept in logarithmic growth or stationary phase. The course of infection could be followed by observing the effect on cells, e.g. viability or syncytia formation, or production of viral components, e.g. antigens or reverse transcriptase. Finally, the minimum time that experiments should be followed in order to be biologically meaningful needs to be determined. All of these factors could affect the evaluation of a given drug.

In order to reduce toxicity and maximise efficacy it will be desirable to identify and use combinations of drugs which are directed against different complementary targets. Reliable *in vitro* work is important before attempting to perform complex trials in humans involving combinations of antiviral drugs, with or without addition of different immunostimulatory agents. A basic methodology, including critical mathematical criteria for the evaluation of synergy or antagonism between drugs, also needs to be incorporated into such experiments (Chou & Talay 1984).

Given the CNS involvement, penetration of the blood-brain barrier has to be taken into consideration, as well as a potential dichotomy between clinical effects on the immune system and the nervous system.

3.2 Planning of Trials

Human trials should preferably be performed in collaborative multicentre studies (e.g. with suramin or zidovudine) conforming to basic protocols in patient selection, dosage schedules, and clinical and laboratory monitoring. This approach will allow rapid identification of the most promising drugs and progression from open phase I studies to the double-blind controlled trials that are a prerequisite for the use of drugs in individuals with early disease and intact immune systems, where they would probably be of greatest benefit. Zidovudine has now become the *de facto* standard for comparison. There is a great urgency to carry out dose-finding studies or determine suitable combinations that might allow the virustatic effect of zidovudine to be balanced against its bone marrow toxicity.

The monitoring of such trials will naturally include drug characteristics such as pharmacokinetics, and clinical and laboratory signs of toxicity. Measurements of effect will be more difficult (for a review see Yarchoan & Broder 1987). Immunological improvements might be looked for by estimating delayed type hypersensitivity, the number or function of T-helper or suppressor cells, responses to mitogens or lectins *in vitro*, or levels of IgG, acid-labile interferon, β_2-microglobulin, interleukin-2 etc. However, patients with advanced stages of the disease might already have irreversible damage of the immune system. Thus, even an effective antiviral agent might be dismissed if we rely solely on these data.

In addition, non-standardised methods of HIV isolation during therapy might reflect our ability to induce and detect HIV *in vitro* rather than the effect of the drug. Capture techniques for free and cell-bound viral antigens and quantitative measurements of proviral DNA need to be developed (Goudsmit et al. 1986; Harper & Marselle 1986; McDougal et al. 1985).

Neurological end-points might prove to be a necessary part of treatment protocols (e.g. brain scans, psychometric tests, or clinical end-points) and may require long term follow-up.

Given the fluctuating course of the disease it will be difficult to establish clinical end-points and acceptable levels of toxicity. The development of the Walter-Reed classification might be a sensitive and useful tool to follow disease progression (Redfield et al. 1986). The incidence of complicating infections or death has proven useful in late stages of the disease in the zidovudine trials, but too insensitive in earlier stages. Thus, double-blind controlled trials with prolonged observation periods of large numbers of treated patients will be needed to establish clinical efficacy, especially in early disease. In countries where zidovudine is available, this drug will be used as the *de facto* standard in trials with AIDS patients. In other countries, clinicians are still faced with the ethical difficulties presented by placebo-controlled double-blind trials.

In the US a task force has now been set up within the Public Health Service to coordinate therapeutic studies (Marwick 1986).

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Authors' address: Dr *Eric Sandström*, Department of Dermatology, Södersjukhuset, 100 64 Stockholm (Sweden).

is *not* given any of the presumptions of section 7(b) of the Act. These include "ownership of the mark," and ownership "imparts prima facie evidence of use." J.C. Hall Co. v. Hallmark Cards, Inc., 52 CCPA 981, 984, 340 F.2d 960, 962, 144 USPQ 435, 437 (1965). Accord, Massey Junior College, Inc. v. Fashion Institute of Technology, 492 F.2d 1399, 1402, 181 USPQ 272, 274 (CCPA 1974). Accordingly, the owner of a mark on the Supplemental Register would have to affirmatively prove use of that mark. See Aloe Creme Laboratories, Inc. v. Bonne Bell, Inc., 168 USPQ 246 (TTAB 1970). This contrasts with the presumption of continuing use of a mark by the owner of a registration on the Principal Register. Gillette Co. v. Kempel, 45 CCPA 920, 921-22, 254 F.2d 402, 404, 117 USPQ 356, 357 (1958).

Court of Customs and Patent Appeals

In re Marshall

No. 77-625 Decided June 30, 1978

PATENTS

1. Patentability — Anticipation — In general (§51.201)

Patentability — Anticipation — Combining references (§51.205)

Rejections under 35 U.S.C. 102 are proper only when claimed subject matter is identically disclosed or described in prior art; in other words, all material elements recited in claim must be found in one unit of prior art to constitute anticipation; In re Samour, 197 USPQ 1, did not disturb this principle.

2. Patentability — Anticipation — In general (§51.201)

Accidental or unwitting duplication of invention cannot constitute anticipation.

3. Patentability — Evidence of — Suggestions of prior art (§51.469)

Patentability — New use or function — In general (§51.551)

Drug's known disadvantages that would naturally discourage search for new uses of that drug may be taken into account in determining obviousness.

Particular patents — Weight Reduction

Marshall, Process for Weight Reduction, rejections of claims 1-9 reversed.

Appeal from Patent and Trademark Office Board of Appeals.

Application for patent of Edward M. Marshall, Serial No. 468,552, filed May 9, 1974. From decision rejecting claims 1-9, applicant appeals. Reversed; Markey, Chief Judge, with whom Baldwin, Judge, joins, dissenting in part, with opinion.

Edward D. O'Brian, Anaheim, Calif., for appellant.

Joseph F. Nakamura (Jack E. Armore, of counsel) for Commissioner of Patents and Trademarks.

Before Markey, Chief Judge, and Rich, Baldwin, Lane, and Miller, Associate Judges.

Lane, Judge.

This is an appeal from the decision of the Patent and Trademark Office (PTO) Board of Appeals (board) sustaining the examiner's rejection under 35 USC 102 of claims 1-4 and entering a new ground of rejection under 37 CFR 1.196(b) of claims 5-9 under 35 USC 103. We reverse both rejections.

Background

Invention

Normally, when food passes through the terminal region of the stomach, nerve endings there stimulate the release of two hormones, secretin and pancreozymin. These hormones then trigger the production and release of pancreatic enzymes necessary for digestion in the small intestine.

Applicant's weight control process involves anesthetizing these nerve endings with an orally administered anesthetic containing 50-2,000 mg of oxethazaine. This prevents the release of secretin and pancreozymin which in turn interferes with the production and release of the pancreatic enzymes. Thus, food passing through the small intestine is not digested and does not contribute calories to the body.

The following claims are before us on appeal:

1. In a weight control process in which a quantity of food is consumed

**icular patents — Weight Reduc-
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hall, Process for Weight Reduc-
jections of claims 1-9 reversed.

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cation for patent of Edward M.
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D. O'Brian, Anaheim, Calif., for
lant.
F. Nakamura (Jack E. Armore, of
el) for Commissioner of Patents
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Background

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ı a weight control process in
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and passes through the gastrointestinal digestive tract of a living body the improvement which comprises:

said quantity of food including foodstuffs requiring digestion caused by pancreatic enzymes for absorption into the bloodstream from the small intestine,

periodically anesthesizing [sic] the nerve endings in the digestive tract which release hormones when contacted by food passing through the digestive tract so as to trigger the release of said pancreatic enzymes into the digestive tract by the pancreas prior to said quantity of food contacting said nerve endings only prior to the passage of food into said digestive tract, said anesthetization being carried out to an extent effective and at a time effective to inhibit said nerve endings from releasing sufficient hormones to cause the release of said pancreatic enzymes which will contact said food as it passes through the digestive tract,

said anesthetization serving to prevent the release of said hormones when said nerve endings are contacted by said quantity of food, this having the effect of preventing release of said enzymes by the pancreas to the digestive tract so that said food passes through the digestive tract without being digested so that it is [sic not] capable of being absorbed into the bloodstream as a consequence of the absence of said enzymes.

2. A weight control process as claimed in claim 1 wherein:

said nerve endings are anesthesized [sic] by orally taking a quantity effective to cause said inhibition of an anesthetic means coated with a coating means which is effective to delay the release of said anesthetic means until said anesthetic means reaches the vicinity of said nerve endings in the digestive tract.

3. A weight control process as claimed in claim 2 wherein:

said anesthetic means is oxethazaine.

4. A weight control process as claimed in claim 2 wherein:

said anesthetic means is orally taken with an adherence means for causing said anesthetic means to adhere to the interior of the digestive tract.

5. A weight control process as claimed in claim 4 wherein:

said adherence means is albumin and is admixed with said anesthetic means, said anesthetic means and said albumin both being coated with said coating means.

6. A weight control process as claimed in claim 2 wherein:

from about 50 to about 2,000 milligrams of said anesthetic means are taken at one time, said time being prior to food being taken into the digestive tract.

7. A weight control process as claimed in claim 2 wherein:

from about 200 to about 800 milligrams of said anesthetic means are taken at one time, said time being prior to food being taken into the digestive tract.

8. A weight control process as claimed in claim 1 wherein:

said nerve endings are anesthesized [sic] by orally taking a quantity effective to cause said inhibition of an anesthetic means coated with a coating which will delay the release of said anesthetic means until said anesthetic means reaches the vicinity of said nerve endings in the digestive tract,

said anesthetic means is oxethazaine, and

from about 50 to about 2,000 milligrams of said anesthetic means are taken at one time, said time being prior to food being taken into the digestive tract.

9. A weight control process as claimed in claim 8 wherein:

said anesthetic means is orally taken with adherence means for causing said anesthetic [sic means] to adhere to the interior of the digestive tract, and

said adherence means is albumin and is admixed with said anesthetic [sic means], said anesthetic [sic means] and said albumin both being coated with said coating.

Prior Art

The reference relied upon are: the PHYSICIAN'S DESK REFERENCE 1522-23 (25th ed. 1971) (PDR); and J. Slayback, E. Swena, J. Thomas, L. Smith, The Pancreatic Secretory Response to Topical Anesthetic Block of the Small Bowel, 61 SURGERY 591 (1967) (Slayback).

The PDR describes drugs containing the anesthetic oxethazaine for the treatment of esophagitis, gastritis, peptic ulcer and irritable colon syndrome. The recommended adult oral dose of these drugs is one or two teaspoons (10-20 mg oxethazaine) four times daily, fifteen minutes before meals and at bedtime. The PDR expressly warns against exceeding the recommended dosage. Regarding the use of these drugs in the treatment of peptic ulcer, the PDR explains that topical appli-

cation of this local anesthetic inhibits the release of the acid-stimulating hormone, gastrin.

Slayback is an article reporting an investigation into the mechanism responsible for the release of the pancreatic secretory hormones, secretin and pancreozymin. Researchers found that application of the anesthetic oxethazaine HCl to isolated segments of the small intestine of surgically altered dogs caused a substantial reduction in the release of both secretin and pancreozymin. These results were consistent with the hypothesis that secretin and pancreozymin release is controlled by a local neural mechanism similar to the one which had been shown to control the release of the gastric secretory hormone, gastrin.

Proceedings Below

The examiner rejected claims 1-4 under 35 USC 102 as anticipated by the PDR and also rejected claims 1-9 under 35 USC 102/103 as anticipated or obvious over a patent to Pober.[1] The board affirmed the 102 rejection of claims 1-4 but reversed the 102/103 rejection of claims 1-9 and entered a new ground of rejection under 37 CFR 1.196(b) rejecting claims 5-9 under 35 USC 103 as obvious in view of the combined teachings of PDR and Slayback.[2]

Opinion

102 Rejection

[1] Rejections under 35 USC 102 are proper only when the claimed subject matter is identically disclosed or described in the prior art. In re Arkley, 59 CCPA 804, 807, 455 F.2d 586, 587, 172 USPQ 524, 526 (1972). In other words, to constitute an anticipation, all material elements recited in a claim must be found in one unit of prior art. Soundscriber Corp. v. United States, 360 F.2d 954, 960, 148 USPQ 298, 301 (Ct.Cl. 1966). This basic principle of patent law has not been disturbed by our recent decision, In re Samour, 571 F.2d 559, 197 USPQ 1 (CCPA 1978), in which we affirmed a §102(b) rejection of claims to a chemical compound based on a primary reference which disclosed the compound and additional references which established that a method of preparing the compound would have been obvious to one skilled in the art. In Samour, every material element of the claimed subject matter, the chemical compound, could be found in the primary reference, a disclosure of that compound.

[2] Applying this rule of law to the present case, we must reverse the board's rejection of claims 1-4 under 35 USC 102 since the primary reference, the PDR, does not disclose every material element of the claimed subject matter. These claims are directed to a weight control process. Applicant uses an effective amount of the anesthetic, oxethazaine, to inhibit release of the pancreatic secretory hormones, secretin and pancreozymin, in order to control weight. The PDR, however, teaches using drugs containing the anesthetic oxethazaine to inhibit release of the acid-stimulating hormone, gastrin, in order to treat esophagitis, gastritis, peptic ulcer and irritable colon syndrome. Nothing in the PDR remotely suggests taking oxethazaine to lose weight. If anyone ever lost weight by following the PDR teachings it was an unrecognized accident. An accidental or unwitting duplication of an invention cannot constitute an anticipation. In re Felton, 484 F.2d 495, 500, 179 USPQ 295, 298 (CCPA 1973).

103 Rejection

The board seems to have combined: (1) the teaching of the PDR that oral administration of oxethazaine inhibits release of gastrin, (2) the teaching of Slayback that secretin and pancreozymin release is controlled by a local neural mechanism similar to the one which controls release of gastrin, and (3) the art-recognized fact that secretin and pancreozymin control the production and release of pancreatic enzymes necessary for digestion in the small intestine, to conclude that applicant's method of controlling weight by anesthetizing the nerve endings that stimulate the release of secretin and pancreozymin would have been obvious.

The problem with this rejection is that nowhere in any reference is there any suggestion to control weight by turning off the production and release of pancreatic enzymes. Although it has long been known that pancreatic enzymes are involved in digestion, from this record it appears that

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[1] U.S. patent No. 3,740,440, issued June 19, 1973, for "Method of Inhibiting Appetite for Food."

[2] The board does not explain why this new ground of rejection was not applied to claims 1-4 as well.

ıical compound based on a pri-
rence which disclosed the com-
d additional references which es-
that a method of preparing the
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applicant is the first to suggest controlling weight by decreasing the quantity of pancreatic enzymes in the small intestine. To say this would have been obvious is to resort to impermissible hindsight.

[3] Moreover, the PDR appears to teach away from using effective amounts of the anesthetic oxethazaine since it expressly cautions against exceeding the recommended dose of 10-20 mg. This would not be an effective amount for controlling weight by appellant's process. Although Slayback, which discusses tests conducted solely on dogs, recognizes that higher concentrations of oxethazaine will produce "complete absence of stimulation of hormonal release," this does not negate the PDR warning with respect to the oral administration to humans. Known disadvantages of a drug which would naturally discourage the search for new uses of that drug may be taken into account in determining obviousness. See United States v. Adams, 383 U.S. 39, 52, 148 USPQ 479, 483-484 (1966).

Accordingly, for the reasons set forth herein, the decision of the board is *reversed.*[3]

Reversed

Markey, Chief Judge, with whom Baldwin, Judge, joins, dissenting in part.

Though I wholeheartedly agree with the majority's treatment of the §102 issue, I respectfully dissent from the majority's conclusion of non-obviousness under §103.

The majority agrees that the board considered "the art recognized fact that secretin and pancreozymin control the production and release of pancreatic enzymes necessary for digestion in the small intestine." Nowhere in the record is there any dispute on that point. Moreover, the majority also recognizes that "it has long been known that pancreatic enzymes are involved in digestion."

Appellant and all others having ordinary skill in the art knew that pancreatic enzymes play a major role in the digestion of food. If food is not digested, it is excreted without being absorbed into the body. If food is not absorbed, the body cannot gain weight. It follows, therefore, that decreasing pancreatic enzyme quantity (or eliminating it altogether) must decrease weight. The particular compound chosen by appellant to shut off or decrease the flow of pancreatic enzymes was known in the art and used for that purpose.

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[3] The board rejected only claims 5-9 under 35 USC 103. In the interest of judicial economy, we note that our reversal of that rejection is not based on any limitations of claims 5-9 not found in broader claims 1-4 as well.

District Court, District of Columbia

Mobil Oil Corporation, et al.
v. Dann, Commissioner of Patents and Trademarks, et al.
No. 76-0021 Decided Feb. 28, 1978

PATENTS

1. Commissioner of Patents — Supervisory authority (§21.30)

Pleading and practice in Patent Office — Rules effect (§54.9)

Commissioner of Patents and Trademarks can grant conditional relief under Patent Rule 183; petitions under that rule are addressed to Commissioner's sound discretion on showing of "extraordinary situation when justice requires"; rule authorizes Commissioner to grant equally flexible forms of relief to do justice according to facts of individual cases due to that inherently flexible standard.

2. Commissioner of Patents — Supervisory authority (§21.30)

Pleading and practice in Patent Office — In general (§54.1)

Commissioner of Patents' action in granting extension of time to applicant that permitted time for appeal or filing civil action to expire following Board of Appeals' affirmance of rejection and sought extension only after learning that assertedly similar application was to be granted competitor, conditioned upon relinquishment of any right to patent on applicant's now-abandoned application, offends no statutory limitation, and fairly accommodates competing interests and equities of parties.

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United States Court of Customs and Patent Appeals.
Application of Herman HOEKSEMA.
Patent Appeal No. 7778.

Aug. 8, 1968.

Proceeding on appeal from a decision of the Patent Office Board of Appeals affirming examiner's rejection of remaining claim of application for a patent on a chemical compound, Serial No. 30,770. The United States Court of Customs and Patent Appeals, 379 F.2d 1007, affirmed. On rehearing, Smith, J., held that application on the chemical compound and a method for the making thereof was patentable over the prior art.

Reversed.

Kirkpatrick, J., dissented.

West Headnotes

[1] **Patents** 16.25
291k16.25 Most Cited Cases
An invention as a whole, for patentability purposes, must be considered as the claimed compound and a way to produce it.

[2] **Patents** 66(1.12)
291k66(1.12) Most Cited Cases
A compound would be considered patentable over the prior art even if the prior art disclosed the claimed compound, where the prior art did not disclose a way to produce it.

[3] **Patents** 16.25
291k16.25 Most Cited Cases
(Formerly 291k18)
If the prior art of record fails to disclose or render obvious a method for making a claimed compound, at time invention was made, it may not be legally concluded that the compound itself is in possession of the public.

[4] **Patents** 32
291k32 Most Cited Cases
Absence of a known or obvious process for making claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds.

[5] **Patents** 66(1.12)
291k66(1.12) Most Cited Cases
Affidavit pointing out that reference relied on as precluding patentability did not disclose a process for producing different compounds claimed was sufficient to overcome cited reference as a patent-defeating reference.

[6] **Patents** 66(1.12)
291k66(1.12) Most Cited Cases
Application on a chemical compound and a method for the making thereof was patentable over the prior art.

Patents 328(2)
291k328(2) Most Cited Cases
3,094,460. Cited.
****270 *1494** Earl C. Spaeth, Kalamazoo, Mich., (Eugene O. Retter, George T. Johannesen, Kalamazoo, Mich., of counsel), for appellant.

Joseph Schimmel, Washington, D.C., (Jack E. Armore, Washington, D.C., of counsel), for Commissioner of Patents.

***1495** Before WORLEY, Chief Judge, and RICH, SMITH, ALMOND and KIRKPATRICK, [FNa1] Judges.

FNa1. Senior District Judge, Eastern District of Pennsylvania, sitting by designation.

SMITH, Judge.

In our prior consideration of this appeal, we affirmed the decision of the Patent Office Board of Appeals, which had affirmed the examiner's rejection of the sole remaining claim of appellant's application, [FN1] In re Hoeksema, 379 F.2d 1007, 54 CCPA 1618 (1967). Bucause of the continuing importance of the questions involved, and the strong suggestion of error in our earlier opinion, we granted appellant's petition for a rehearing under the provisions of Rule 7 of this court, 55 CCPA , (October 5, 1967).

FN1. Claim 1 in Serial No. 30770, filed May 23, 1960, for '9-D-Psicofuranosylpurine and 6-Substituted Derivatives.' Claims 2 and 11-25 stand allowed.

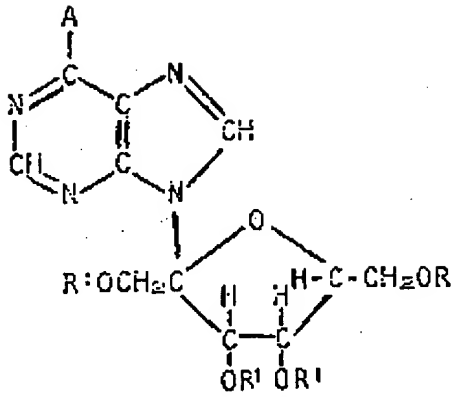
The parties filed new briefs, and the case was reargued on January 3, 1968. Upon reconsideration of our previous decision, we have concluded that our previous decision was erroneous and that a proper resolution of the issues requires that we reverse the

decision of the board.

The facts are set forth in our original opinion. We shall assume familiarity with that statement of facts and shall here redevelop only those which we now believe were previously misapprehended or misapplied and require the present decision.

The sole claim on appeal is directed to a chemical compound and reads as follows:

1. An N-psicofuranside having the formula:



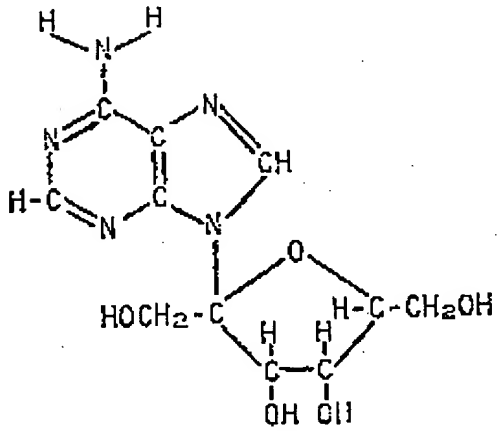
wherein A is selected from the class consisting of hydrogen, the group-XR wherein R is selected from the class consisting of hydrogen, lower-alkyl, and lower-aralkyl, and X is selected from the class consisting of oxygen

R sub2
and sulfur, and the group -- N <
R sub3

wherein R(2) is selected from the class consisting of hydrogen, lower-alkyl, lower-aralkyl, and lower-aryl, and R(3) is selected from the class consisting of lower-alkyl, lower-aralkyl, and lower-aryl, and R' is selected from ***1496** the class consisting of hydrogen, a hydrocarbon carboxylic acid acyl radical containing from two to twelve carbon atoms, inclusive, and a halo-, hydroxy-, lower-alkoxy-, amino-, cyano-, thiocyano-, and nitro-substituted hydrocarbon carboxylic acid acyl ****271** radical containing from two to twelve carbon atoms, inclusive.

That claim stands rejected under 35 U.S.C. § 103 as unpatentable over prior art, on this record limited solely to the De Boer et al. patent [FN2] (De Boer) which discloses a compound with the structural formula:

> FN2. Patent No. 3,094,460, issued June 18, 1963 on an application filed January 20, 1959.



As we noted in our original opinion, the controversy here is limited to the substituent A at the 6-position of the purine ring system. Although a compound having De Boer's structure is not included in the appealed claim since A in the claim cannot be an unsubstituted or primary amino,

H
-- N <
H ,

the basic structure of the De Boer compound is similar to the structure of appellant's alkyl-amino and dialkylamino compounds. [FN3]

> FN3. Appellant, in effect, admits that there is such a 'structural similarity' between his claimed compounds and the prior art compounds as to raise an 'inference of fact' that they are not patentable within the meaning of 35 U.S.C. § 103. See In re Papesch, 315 F.2d 381, 50 CCPA 1084 (1963); In re Mills, 281 F.2d 218, 47 CCPA 1185 (1960).

Despite this close structural similarity between the De Boer amino compound and the alkylamino and dialkylamino compounds included in the appealed claim, appellant chose not to submit a showing of unexpected properties in his claimed compounds. [FN4] Appellant asserted that his compounds were unobvious and patentable without such a showing. He urged that De Boer does not teach one of ordinary skill in the art how to make appellant's claimed compounds, and the examiner did not cite any other reference telling how they might be made. Therefore, in appellant's view, his claimed compounds are not ***1497** in possession of the public, In re Brown, 329 F.2d 1006, 51 CCPA 1254 (1964). [FN5]

> FN4. Such a showing often has been treated by this court as overcoming a case of 'prima facie obviousness' or the 'inference of fact' that the compounds are obvious. See, e.g., In re Papesch, supra note 3 and cases cited therein.

> FN5. For the applicability of In re Brown, supra, to other factual contexts, see In re Bird, 344 F.2d 979, 982, 52 CCPA 1290, 1294 (1965); In re Sheppard, 339 F.2d 238, 242, 52 CCPA 859, 864 (1964); Dix-Seal Corp. v. New Haven Trap Rock Co., 236 F.Supp. 914, 921 (D.C.Conn. 1964).

In support of his position, appellant submitted an affidavit by Dr. Paul F. Wiley relating to the unavailability to the public of processes for preparing appellant's alkylamino and dialkylamino compounds. [FN6] Dr. Wiley's qualifications ****272** and competence as an expert to state facts and opinion in this area of chemistry were not challenged.

> FN6. After setting forth his qualifications and stating that he had read and understood both appellant's application and the prior art patent, Dr. Wiley stated: THAT, 6-amino-9-D-psicofuranosylpurine is a systematic name for 'psicofuranine' which is disclosed in column 6, lines 46-62 of the aforesaid patent;
> THAT, according to the aforesaid patent, 6-amino-9-D-psicofuranosylpurine is produced by a fermentation process involving the action of a specific microorganism, S. hygroscopicus var. decoyinine, in certain aqueous nutrient media;
> THAT, there is no indication in the aforesaid patent (De Boer) that the aforesaid fermentation process could be used to produce 6-lower-alkylamio - 9 - D - psicofuranosylpurines, 6 - di - lower - alkylamino - 9 - D - psicofuranosylpurines, or other 6-substituted - amino - 9 - D - psicofuranosylpurines;
> THAT, he does not believe the aforesaid fermentation process could be adapted to the production of the aforesaid 6-lower-alkylamino-9-D-psicofuranosylpurines, 6-di-lower-alkylamino-9-D-psicofuranosylpurines, or other 6-substituted - amino - 9 - D - psicofuranosylpurines;
> THAT, the aforesaid 6-amino-9-psicofuranosylpurine could not be transformed by direct chemical substitution of the 6-amino group to a 6 - lower - alkylamino 9 - D - psicofuranosylpurine, a 6-di-lower alkylamino-9-D-psicofuranosylpurine, or other 6-substituted - amino - 9 - D - psicofuranosylpurines, and that such transformations could be carried out only by a complex multi-step procedure such as that described in the aforesaid patent application Serial No. 30,770. (Emphasis added.)

Regarding the Wiley affidavit, the examiner stated, in his Answer:

The affidavit * * * does not appear to be pertinent to the claim now on appeal because it is directed to the processes by which the De Boer et al. and appellant's compounds are prepared, and shows nothing unobvious for the instantly claimed compound.

Concerning the Wiley affidavit, the board cited a statement of this court in In re Riden, 318 F.2d 761, 50 CCPA 1411 (1963), to the effect that 'the method of making the compounds is a relevant fact to be considered in the question of obviousness of the compounds,' 318 F.2d at 764, 50 CCPA at 1415. But the board continued:

* * * This may be so but it is only one factor and, in our opinion, should never be the overriding one which appellant is here, in effect, urging.

Appellant states the first of two central questions to be decided in this rehearing as follows:

1) Appellant will admit his compounds are obvious and unpatentable if an obvious process is available to make them. Does it follow then that appellant's compounds are unobvious and patentable if an obvious process is not available to make them?

***1498** Within this context, appellant simplifies that question to: Is process obviousness relevant in deciding compound obviousness? [FN7]

> FN7. To this extent, appellant has misstated his argument. That process obviousness is relevant in this context is clear from In re Riden, supra. See also In re Chapman, 357 F.2d 418, 53 CCPA 978 (1966); In re Burt, 356 F.2d 115, 53 CCPA 929 (1966); In re Schechter, 205 F.2d 185, 40 CCPA 1009 (1963).
> We think appellant really means to say that the question is whether a claimed compound may be said to be legally obvious when no process for making that compound is shown in the prior art relied upon to establish legal obviousness under section 103.

The solicitor responds to the latter characterization of the question in the affirmative, pointing out that the first question bears on the principle implicit in In re Brown, supra, that claimed compounds not distinguished in their properties over closely related prior art compounds are unpatentable thereover where the claimed compounds would be 'in possession of the public' in that a process for preparing them would be obvious to those of ordinary skill in the art.

In addition, the solicitor now refers to our prior opinion in which we noted that the facts in this case are closely analogous to those of In re Riden, supra, where we stated that the fact that the method of making the claimed compound is relevant, 379 F.2d at 1010, 54 CCPA at .

A recurring problem of analysis which confronted us as we prepared our previous opinion, and which still confronts us after the rehearing, has its genesis in a proper understanding of the issue as framed by appellant. In effect, appellant agrees that since the claimed product ****273** is a homolog of a known compound, it would be prima facie 'obvious' under 35 U.S.C. § 103. But this agreement is conditioned on the proviso that there is in the prior art an 'obvious' process by which to make that compound.

In the context of section 103, we are not permitted to fragment a claimed invention in applying that section. The clear mandate of the statute which governs our analysis requires that we consider the invention as a whole in making the determination.

Thus, as we apply the statute to the present invention, we must ask first, what is the invention as a whole? Necessarily, by elementary patent law principles, it is the claimed compound, but, so considered, unless there is some known or obvious way to make the compound, the invention is nothing more than a mental concept expressed in chemical terms and formulae on a paper.

[1] We are certain, however, that the invention as a whole is the claimed compound and a way to produce it, wherefore appellant's argument has substance. There has been no showing by the Patent Office in this record that the claimed compound can exist because there is no showing of a known or obvious way to manufacture it; hence, it seems to ***1499** us that the 'invention as a whole,' which section 103 demands that we consider, is not obvious from the prior art of record.

[2] While there are valid reasons based in public policy as to why this defect in the prior art precludes a finding of obviousness under section 103, In re Brown, supra, its immediate significance in the present inquiry is that it poses yet another difference between the claimed invention and the prior art which must be considered in the context of section 103. So considered, we think the differences between appellant's invention as a whole and the prior art are such that the claimed invention would not be obvious within the contemplation of 35 U.S.C. § 103.

While 35 U.S.C. § 102 is not directly involved in the issue on review, the conditions for patentability, novelty and loss of right to patent, there stated, may have relevance as to the disclosure which must be found in the prior art to find obviousness of an invention under section 103. In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure,' in the present context, a process by which the claimed compound could be made. In In re Le Grice, 301 F.2d 929, 49 CCPA 1124 (1962), we observed that the resolution of this issue required us to determine whether, as a matter of law, a reference without such a disclosure constituted a statutory time bar to an applicant's right to a patent. There, the issue was founded on 35 U.S.C. § 102(b), not § 103, but our conclusions have a certain pertinence here. We concluded, id. 301 F.2d at 936, 49 CCPA at 1134:

We think it is sound law, consistent with the public policy underlying our patent law, that before any publication can amount to a statutory bar to the grant of a

patent, its disclosure must be such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention. * * *

In In re Brown, supra, this court discussed In re Von Bramer, 127 F.2d 149, 29 CCPA 1018 (1942), commenting that that opinion should not be construed to emcompass what had come to be called the 'Von Bramer doctrine.' There we stated, 329 F.2d at 1009, 51 CCPA at 1257:

* * * This doctrine, which appears to have resulted from In re Von Bramer et al., supra, seems over a period of years to have been tailored in some quarters to a principle which defeats the novelty of a chemical compound on the basis of a mere printed conception or a mere printed contemplation of a ****274** chemical 'compound' irrespective of the fact that the so-called 'compound' described in the reference is not in existence or that there is no process shown in the reference for preparing the compound, or that there is no process ***1500** known to a person having ordinary skill in the relevant art for preparing the compound. In other words a mere formula or a mere sequence of letters which constitute the designation of a 'compound,' is considered adequate to show that a compound in an application before the Patent Office, which compound is designated by the same formula or the same sequence of letters, is old. We do not think that the Von Bramer case should be so construed. (Emphasis added.)

To the extent that anyone may draw an inference from the Von Bramer case that the mere printed conception or the mere printed contemplation which constitutes the designation of a 'compound' is sufficient to show that such a compound is old, regardless of whether the compound is involved in a 35 U.S.C. § 102 or 35 U.S.C. § 103 rejection, we totally disagree. * * *

We concluded, relying on In re Le Grice, supra, and E. I. DuPont de Nemours & Co. v. Ladd, 117 U.S.App.D.C. 246, 328 F.2d 547 (1964), that the 'true test of any prior art relied on to show or suggest that a chemical compound is old, is whether the prior art is such as to place the disclosed 'compound' in the possession of the public.' 329 F.2d at 1011, 51 CCPA at 1259.

While In re Le Grice was bottomed on an issue arising under 35 U.S.C. § 102 where the reference was a 'printed publication,' that test, in our view, is also properly applicable to issues arising under 35 U.S.C. § 103. See In re Brown, supra (pertinent portion quoted above); Deutsche Gold-Und Silber-Scheideanstalt v. Commissioner of Patents, 251 F.Supp. 624, 629-630 (D.D.C.1966), affirmed, 397 F.2d 656 (D.C.Cir. 1968).

[3][4] Thus, upon careful reconsideration it is our view that if the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. [FN8] In this context, we say that the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds.

> FN8. In Phillips Petroleum Co. v. Ladd, 219 F.Supp. 366 (D.D.C.1963), in considering a rejection arising under 35 U.S.C. § 102, the District Court agreed with this court that the mere naked statement of the invention does not put anyone in possession of the invention. That court was careful to note that no process had been shown in the reference for preparing the compound and that no process was known to one of ordinary skill in the art for preparing the compound.
> In Ex parte Wall, 156 USPQ 95 (P.O.Bd.App.1964), the board, considered a rejection under 35 U.S.C. § 102 of a claim reading 'Perfluorostyrene.' In reversing the examiner, the board commented that the examiner did not contend that the reference disclosed how perfluorostyrene is made, nor did he point to any extraneous evidence which would indicate that those skilled in the art knew how to make that compound.

The second aspect of the questions presented by this rehearing involves ***1501** the issue of whether the burden is on the Patent Office to provide the evidence on which to predicate process obviousness.

35 U.S.C. § 101 states, in its preamble, that an applicant is entitled to a patent unless certain patent-defeating provisions are met. The substantive patent-defeating provisions are encompassed in 35 U.S.C. § § 100-103.

As we have stated, the Patent Office search resulted in citation of the De Boer reference which, under the prevailing law, rendered appellant's claimed compounds prima facie obvious. In other ****275** words, its citation shifted to appellant the burden of going forward with contrary evidence. Appellant filed the affidavit of Dr. Wiley which points out as a fact that De Boer-- the only reference being relied on-- does not disclose a process for producing the different compounds here claimed.

[5] We think that portion of the Wiley affidavit set forth, supra note 6, states facts which were legally sufficient to overcome the position of the Patent Office as to the legal effect under section 103 of the De Boer reference. [FN9] Appellant's responsibility to overcome this reference as a 'patent-defeating' reference under section 103 at that point in the prosecution was only to overcome De Boer as a reference pertinent to the issue of obviousness under section 103.

> FN9. We think this approach to be eminently fair to all parties and in accord with the opinion of the Supreme Court in Graham, in its requiring that all of the pertinent evidence be considered while yet leaving the primary responsibility for sifting out unpatentable material with the Patent Office, Graham v. John Deere Co., 383 U.S. 1 at 18, 86 S.Ct. 684, 15 L.Ed.2d 545.
> It would be practically impossible for an applicant to show that all known processes are incapable of producing the claimed compound.

We think the Wiley affidavit is clearly sufficient for this purpose. The affidavit points out that there is no indication in the De Boer patent that the fermentation process used to produce De Boer's compounds could be used to produce appellant's compounds. Since we are of the view that the method for making the compounds is an integral part of the 'invention as a whole' which we must consider under section 103, we conclude that the burden of going forward with proofs to support its position as to obviousness of the claimed invention shifted to the Patent Office upon appellant's filing of the Wiley affidavit.

[6] The failure of the Patent Office to produce such evidence requires that the decision of the board be reversed.

***1494** Reversed.

***1501** WORLEY, C.J., did not participate.

KIRKPATRICK, Judge (dissenting).

I am unable to agree with the result reached by the majority. The reasons for my dissent appear in the overruled opinion In re Hoeksema, 379 F.2d 1007, 54 CCPA 1618 (1967).

55 C.C.P.A. 1493, 399 F.2d 269, 158 U.S.P.Q. 596

END OF DOCUMENT

United States Court of Customs and Patent Appeals.
Application of Joseph D. FISHER.
Patent Appeal No. 8208.

June 11, 1970.

Appeal from decision of the Board of Appeals of the United States Patent Office, serial No. 72,481, rejecting claims of an application for a patent on an adrenal gland stimulating concentrate. The Court of Customs and Patent Appeals, Lane, J., held that claims four and five for patent for adrenal gland stimulating concentrate were properly rejected for insufficient disclosure and claim four was properly rejected on ground of anticipation by published references.

Affirmed.

West Headnotes

[1] **Patents** 66(1.12)
291k66(1.12) Most Cited Cases
Inventor of medical composition will be allowed to dominate future compositions having potencies far in excess of those obtainable from his teachings plus ordinary skill where those inventions were based in some way on his teachings, provided that his claims were sufficiently supported. 35 U.S.C.A. § 112.

[2] **Patents** 66(1.12)
291k66(1.12) Most Cited Cases
Claims four and five for patent for adrenal gland stimulating concentrate were properly rejected for insufficient disclosure and claim four was properly rejected on ground of anticipation by published references. 35 U.S.C.A. § § 102, 112.

Patents 328(2)
291k328(2) Most Cited Cases
3,192,115. Cited.
****834 *1100** Carl C. Batz, Frank T. Barber, Chicago, Ill., attorneys of record, for appellant. George R. Jones, Robert H. Berdo, Beale & Jones, Arlington, Va., of counsel.

Joseph Schimmel, Washington, D.C., for the Commissioner of Patents. Jack E. Armore, Washington, D.C., of counsel.

Before RICH, Acting Chief Judge, ALMOND, BALDWIN, and LANE, Judges, and MATTHEWS, Senior Judge, United States District Court for the District of Columbia, sitting by designation.

LANE, Judge.

This appeal is from the decision of the Patent Office Board of Appeals, which affirmed the rejection of claims 4 and 5, the only claims remaining in appellant's application serial No. 72,481, filed November 29, 1960, for Adrenal Gland Stimulating Concentrate and Method for the Preparation Thereof. The application is a continuation-in-part of a prior co-pending application serial No. 435,451, filed June 9, 1954, which was before this court in In re Fisher, 307 F.2d 948, 50 CCPA 1025 (1962). That application was a continuation of application serial No. 122,588, filed October 20, 1949, which we shall refer to as the parent application.

THE DISCLOSURE

The instant specification relates to the preparation of substances containing adrenocorticotrophic hormones (ACTH) in a composition suitable for injection into human beings in the treatment of certain forms of arthritis and other human pathological conditions. It is stated that previous ACTH products were unsatisfactory for administration to humans because of their low potency, generally around ***1101** 50% Of 'International Standard,' and because of their relatively high content of undesirable factors, notably posterior pituitary hormones which consist mainly of oxytocic and vasopressor principles. A method [FN1] is disclosed for producing ACTH preparations having potencies ranging from 111% To 230% Of standard and containing no more than 0.08 units of vasopressin and no more than 0.05 units of oxytocin per International Unit of ACTH, which limits are said to be tolerable to humans. The method generally starts with frozen pituitary glands of hogs, sheep, beef or other animals, including whales. These glands are quick-thawed in an organic solvent to extract contaminated ACTH from the gland meat. A precipitate containing the active material is recovered, free of contaminants, by treatment with fractionating salts. The material is then subjected to hydrolysis, and an inactive fraction of hydrolized fragmented material is separated from a fraction containing the active substance. The active fraction is then adjusted to a pH above 2.8, the excess salts being separated from the concentrate of the active principle. Several variations of this procedure are set forth and six specific examples are given. The specification then states that the ACTH concentrate produced as described is found to contain peptides having free amino and carboxyl groups, and is further

characterized

> FN1. The method is said to be covered by appellant's patent 3,192,115, issued June 29, 1965.

by its solubility in glacial acetic acid and phenol; by its relative insolubility in other organic solvents; by its greater stability under acid conditions than under alkali conditions; by its susceptibility to attack by proteolytic enzymes and peptidases; and by its positive reaction to the Millon and xanthoproteic tests for tyrosine, the biuret test for peptide linkage, the ninhydrin test for free amino groups in the alpha position, the Sakaguchi test for guanidine groups, and the Hopkins-Gole and benzaldehyde tests for indole nuclei and tryptophane.

The specification then states that the product can be characterized structurally as a peptide containing a chain of identifiable amino acids. While the exact sequence will vary from product to product, depending on the source and preparative history of the product, the first 24 ****835** amino acids in the chain, counting from the N terminus of the molecule, will have the following sequence: (1) Serine, (2) Tyrosine, (3) Serine, (4) Methionine, (5) Glutamic Acid, (6) Histadine, (7) Phenylalanine, (8) Arginine, (9) Tryptophan, (10) Glycine, (11) Lysine, (12) Proline, (13) Valine, (14) Glycine, (15) Lysine, (s6) Lysine, (17) Arginine, (18) Arginine, (19) Proline, (20) Valine, (21) Lysine, (22) Valine, (23) Tyrosine, (24) Proline. ACTH obtained from hogs contains a sequence of 39 amino acids, the first 24 being as recited above; ACTH obtained from sheep or beef also contains a sequence of 39 amino acids, the first 24 being as recited, and the 25th to ***1102** 39th being in a sequence different from that of the hog extract. [FN2] No structural description is given for ACTH extracted from other animals.

> FN2. The 25-to-39 sequence for sheep is set forth, but for beef the sequence is apparently unknown. It is stated that the empirical formula for beef and sheep ACTH is the same.

THE CLAIMS

Appellant defines the subject matter sought to be patented as follows:

4. An adrenocorticotrophic hormone preparation containing at least 1 International Unit of ACTH per milligram and containing no more than 0.08 units of vasopressin and no more than 0.05 units of oxytocin per International Unit of ACTH, and being further characterized as containing as the active component of (a?) polypeptide of at least 24 amino acids having the following sequence from the N terminus of the molecule; Serine, Tyrosine, Serine, Methionine, Glutamic Acid, Histadine, Phenylalanine, Arginine, Tryptophan, Glycine, Lysine, Proline, Valine, Glycine, Lysine, Lysine, Arginine, Arginine, Proline, Valine, Lysine, Valine, Tyrosine, Proline.

5. An adrenocorticotrophic hormone preparation containing at least 1 International Unit of ACTH per milligram and containing no more than 0.08 units of vasopressin and no more than 0.05 units of oxytocin per International Unit of ACTH, and being further characterized by its solubility in glacial acetic acid and phenol; by its relative insolubility in other organic solvents; by its greater stability under acid conditions than under alkali conditions; by its susceptibility to attack by proteolitic enzymes and peptidases; and by its positive reaction to the Millon and xanthoproteic tests for tyrosine, the biuret test for peptide linkages, and the ninhydrin test for free amino groups in the alpha position, the Sakaguchi test for guanidine groups, and the Hopkins-Gole and benzaldehyde tests for indole nuclei and tryptophane.

OPINION

There are many grounds of rejection affirmed by the board in this case. We shall set them forth separately, with our opinion on each.

(a) The res judicata rejection

The board affirmed the examiner's rejection of claim 5 on the ground of res judicata, stating that the claim differed from claim 13 in Fisher, supra, 'mainly in calling for a 'preparation containing at least 1 International Unit of ACTH per milligram' in place of the terminology in claim 13 'concentrate having a potency at least equal to that of the International Standard.'" The board held this to be 'no significant difference other than in verbiage.' We reverse the board on this ground of rejection. 'Verbiage' was the very problem in Fisher. The court there found that the words 'a potency at least equal to the International Standard' rendered the claims unpatentable under the second paragraph of 35 U.S.C. § 112. 307 F.2d at 950-951, 50 CCPA at 1029. ***1103** These words do not appear in the claims before us. Thus, a different issue is presented and res judicata does not apply. See In re Fried, 312 F.2d 930, 50 CCPA 954 (1963).

**836 (b) The rejection on the Li references

The examiner rejected claim 4 under 35 U.S.C. § 102 as anticipated by the following references:

Li et al. (III), Science, vol. 124, p. 934 (Nov. 9, 1956).

Li et al., J.A.C.S., vol. 80, No. 10, pp. 2587-88 (May 20, 1958).

Appellant did not contest the pertinence of these references, but sought to remove them by relying on his parent application which, as mentioned above, was filed in 1949. The examiner took the position that appellant was not entitled to the parent date under 35 U.S.C. § 120 because the parent contained insufficient disclosure to support claim 4 in the manner required by the first paragraph of 35 U.S.C. § 112. The board affirmed this rejection for two reasons. First, since the parent application lacked any structural description of the ACTH extracts therein disclosed, the Board concluded that it could not be determined whether those products would meet the terms of claim 4, which recites a specific sequence of the first 24 amino acids. Appellant contended that the parent application inherently disclosed products meeting the terms of claim 4, even though appellant did not know the chemical structure of those products when the parent application was filed. Appellant cited several cases in support of the proposition that inherent disclosure is sufficient under 35 U.S.C. § 112, including Riester v. Kendall, 159 F.2d 732, 34 CCPA 859 (1947), and In re Nathan, 328 F.2d 1005, 51 CCPA 1059 (1964). The board did not dispute the correctness of this proposition, but found that 'it has not been established that the parent disclosures inherently produce the claimed products * * *.' We agree with appellant that this finding was erroneous. The parent application discloses treatment of hog pituitary extracts. The Li (J.A.C.S.) article discloses the amino acid sequence for beef ACTH and states that the first 24 amino acids in the sequence are the same for porcine (hog) ACTH, namely, the sequence recited in claim 4. The hog-extracted products disclosed in appellant's parent application must therefore have had the recited sequence. The board's second reason for holding the parent application insufficient to support claim 4 was not the products disclosed in the parent were insufficient to support a claim of the breadth of claim 4. On this point we agree with the board. The claim recites that the product must contain 'at least' 24 amino acids in a specified sequence. The parent disclosure mentions treating extracts from 'hog, beef, lamb, and other animal pituitary glands, and including also pituitary *1104 glands of whales.' From the instant specification and the Li articles, we know that hog, beef and lamb ACTHs will contain 39 amino acids, of which the first 24 will be in the recited sequence. We do not know, from the record, the chemical structure of ACTHs of whales or other animals. Appellant's parent application, therefore, discloses no products, inherently or expressly, containing other than 39 amino acids, yet the claim includes all polypeptides, of the recited potency and purity, having at least 24 amino acids in the chain in the recited sequence. The parent specification does not enable one skilled in the art to make or obtain ACTHs with other than 39 amino acids in the chain, and there has been no showing that one of ordinary skill would have known how to make or obtain such other ACTHs without undue experimentation. As for appellant's conclusion that the 25th to 39th acids in the chain are unnecessary, it is one thing to make such a statement when persons skilled in the art are able to make or obtain ACTH having other than 39 amino acids; it is quite another thing when they are not able to do so. In the latter situation, the statement is in no way 'enabling' and hence lends no further support for the broad claim. We conclude that appellant's parent application is insufficient to support a claim as broad as claim 4. For this reason we affirm the board's rejection of claim 4 as unpatentable over the Li references.

**837 (c) The rejection on Collip

The examiner rejected both claims under 35 U.S.C. § 102 as unpatentable over Collip, 'Properties of Anterior Lobe Extracts,' Symposia Quant. Biol., vol. 5, pp. 210-12 (1937). The examiner's position was that, although Collip does not expressly anticipate the claims, Collip and appellant prepare their ACTH under identical conditions, and it follows that the products producted are identical. The board noted that Judge Smith's dissenting opinion in Fisher, supra, expressed the view that Collip did not render similar product claims obvious under 35 U.S.C. § 103. The majority in Fisher did not reach that issue. The board here concluded, however, that the examiner's rejection on Collip under 35 U.S.C. § 102 was correct. The board stated: 'Since the claim terminology is not sufficiently definite to positively distinguish over the products inherently produced by following the Collip disclosure, this rejection will be sustained.' Appellant contends, and we agree, that Collip is deficient in so many material respects that it cannot be reasonably concluded that it discloses anything like the compositions here claimed. There

is substantial doubt as to whether Collip uses a pH less than 3.0. The doubt arises because the pH at the origin of a Collip graph of pH vs. weight of adrenals is not indicated by a numeral. The solicitor contends that this point represents a pH of 1.0. ***1105** Appellant contends that it is merely a control point, and supports this contention by observing that controls are stated on the graph and that, if a pH of less than 3.0 were actually used, an increase of activity should result, as taught by appellant, rather than a decrease as indicated by the Collip graph. Further, as pointed out by Judge Smith, Collip describes experiments on rats and guinea pigs, and there is no indication that the vasopressin and oxytocin levels in the Collip products were within the safe-for-humans levels which are recited in the claims and which are an important aspect of appellant's contribution to the art. In view of these deficiencies, we believe appellant was not obliged to present comparative evidence to rebut the Patent Office position on the inherent disclosure of Collip. We reverse the board's affirmance of the rejections on Collip.

(d) The indefiniteness rejection

The examiner rejected both claims for indefiniteness under the second paragraph of 35 U.S.C. § 112. He stated:

Claim 4 is indefinite in not setting forth the entire composition chemically. It would appear that the amino acid sequence is only part of the chemical structure of the composition. Claims 4 and 5 are indefinite in not setting forth with particularity the chemical structure or adequate physical characteristics to identify the composition. * * *.

The board affirmed the indefiniteness rejection and gave reasons in addition to those stated by the examiner. We find that the claims before us are in compliance with the second paragraph of section 112 and that the board's affirmance of the indefiniteness rejection must be reversed. We shall discuss each reason given by the board.

The board first found that some of the issues were the same as those treated by the board in the earlier Fisher case involving appellant's earlier application. The board here quoted several pages from its earlier opinion, the gist of which appears to be that the claims there involved, which recited no chemical structure, were indefinite in that the potency and purity limitations there recited were inadequate to enable a decision to be made as to patentability over the prior art. The criticism of the use of the word 'potency' was affirmed by this court in Fisher, supra. The word does not appear in the claims before us. The relevance of the quoted portion of the board's earlier opinion therefore appears to be with regard to the expression appearing in the present claims: 'Containing at least 1 International Unit of ACTH per milligram ****838** and containing no more than 0.08 units of vasopressin and no more than 0.05 units of oxytocin per International Unit of ACTH.' The specification states that 'International Standard' means the generally accepted standard adopted by The Technical ***1106** Advisory Committee to the Study Section for Metabolism and Endocrinology of the National Institutes of Health, and that one milligram of the standard equals one International Unit. We fail to see anything indefinite in such a recitation. We recognize a problem in determining differences over the prior art where the claim uses language which is now accepted and precise but which was not used in the art at the time the prior-art references were published. However, were we to require that claims speak in the language of the prior art, we would be prohibiting the use of the newer and frequently more precise language of the present art. We think that the proper solution to this problem is to allow the use of new expressions when they are definite, and to allow the Patent Office, as it has always done, to call for comparative evidence when there is reason to believe that the prior art discloses matter which renders the claimed subject matter old or obvious.

The board next agreed with the examiner that 'the claims are so broad as to be indefinite in that they do not positively identify the entire chemical structure of the compound desired to be claimed.' The board noted that claim 4 recited only a portion of the molecule, namely at least 24 amino acids in a certain sequence, 'which does not describe adequately the products formed in appellant's specification.' Here the examiner and the board have viewed the absence of a limitation as to amino acids beyond the 24th position as rendering the claim indefinite. While the absence of such a limitation obviously broadens the claim and raises questions of sufficiency of disclosure, it does not render the claim indefinite. The absence of the limitation has a precise meaning. Regardless of the specification, the claimed subject matter is in no way limited by the presence, absence or sequence of amino acids beyond the 24th position. This principle is the very basis of this court's consistent refusal to read limitations of the specification into the claims. See In re Prater, 415 F.2d 1393, 56 CCPA 1381 (1969), and cases therein

cited. In our recent decision in In re Wakefield, 422 F.2d 897, 57 CCPA (1970), we considered an indefiniteness rejection involving the absence of a limitation. We reversed the rejection, stating: 'The scope of the claim is still definite, however, because each recited limitation is definite.'

The board also found indefiniteness in the fact that the claims were not limited to compositions disclosed or suggested by appellant's specification, and would cover 'a host of materials produced in any possible manner, including synthetically, which are neither taught nor represented by the specific materials actually formed in appellant's examples.' Appellant does not dispute that the claims are as broad as the board indicated. This fact, however, while very important ***1107** in assessing the sufficiency of appellant's disclosure to see if it will support such broad coverage, is entirely irrelevant to the issue of definiteness, for the reasons stated in the preceding paragraph.

We conclude that the board's affirmance of the rejection of the claims for indefiniteness under the second paragraph of 35 U.S.C. § 112 must be reversed.

(e) The rejection for insufficient disclosure

The examiner did not reject the claims for insufficient disclosure. This was first applied by the board, although the board failed to denominate it a new ground of rejection under Rule 196(b). Appellant apparently did not complain of such failure, but chose to appeal here.

The board stated: 'We consider appellant's claims to be so broad that * * * the specification lacks sufficient supporting description to comply with the requirements of 35 U.S.C. § 112, first ****839** paragraph.' The board noted that the claims cover

substantially all 'preparations' produced synthetically or by breakdown of the 39 amino acid polypeptides in any manner to form a polypeptide product of lesser molecular weight containing any number (claim 5) or at least 24 (claim 4) of the amino acids as long as the product exhibits, without the stated side effects, activity equal to at least 1 International Unit of ACTH per milligram.

We have already discussed, with respect to the parent application, the lack of teaching of how to obtain other-than-39 amino acid ACTHs. That discussion is fully applicable to the instant application, and we think the board was correct in finding insufficient disclosure due to this broad aspect of the claims.

The second aspect of breadth mentioned by the board in the quoted portion of its opinion has not yet been discussed. This is the problem arising from the potency recitation 'at least 1 International Unit of ACTH per milligram.' This is a so-called 'open-ended' recitation. It has a lower limit but no upper limit. As previously mentioned, the specification discloses products having potencies from 111% To 230% Of standard, which we understand to mean from 1.11 to 2.30 International Units of ATCH activity per milligram. The issue thus presented is whether an inventory who is the first to achieve a potency of greater than 1.0 for certain types of compositions, which potency was long desired because of its beneficial effect on humans, should be allowed to dominate all such compositions having potencies greater than 1.0, including future compositions having potencies far in excess of those obtainable from his teachings plus ordinary skill.

***1108** [1][2] It is apparent that such an inventor should be allowed to dominate the future patentable inventions of others where those inventions were based in some way on hit teachings. Such improvements, while unobvious from his teachings, are will within his contribution, since the improvement was made possible by his work. It is equally apparent, however, that he must not be permitted to achieve this dominance by claims which are insufficiently supported and hence not in compliance with the first paragraph of 35 U.S.C. § 112. That paragraph requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved. In the present case we must conclude, on the record before us, that appellant has not enabled the preparation of ACTHs having potencies much greater than 2.3, and the claim recitations of potency of 'at least 1' render the claims insufficiently supported under the first paragraph of 35 U.S.C. § 112.

Our conclusion is in no way opposed to the principles of the cases cited by appellant in support of his contention that he is entitled to coverage of the breadth now sought. Farbenfabriken of Elberfeld Co. v. Kuehmsted ('the aspirin case'), 171 F. 887 (N.D.Ill.1909), affd. 179 F. 701, 103 CCA 243 (7th Cir. 1910); In re Williams, 171 F.2d 319, 36 CCPA 756 (1948), and Parke, Davis & Co. v. H. K. Mulford & Co., 196 F. 496, 166 CCA 262 (2d Cir. 1912), each involved claims to substantially pure compositions. Such claims do not present the same breadth problem as here, because in those cases the possible range of further purification was either small or nonexistent. Such claims have an inherent upper limit of ****840** 100% Purity, whereas in the present case it would appear theoretically possible to achieve potencies far greater than those obtained by appellant. Merck & Co. v. Olin Mathieson Chemical Corp., 253 F.2d 156 (4th Cir. 1958), involved a claim reciting an activity of 'at least 440 L.L.D. units per milligram,' but no issue appears to have been raised regarding that recitation and the court's opinion does not consider it.

For the reasons given above, the decision of the board is affirmed.

***1100** Affirmed.

57 C.C.P.A. 1099, 427 F.2d 833, 166 U.S.P.Q. 18

END OF DOCUMENT

□

Briefs and Other Related Documents

United States Court of Appeals,
Federal Circuit.
In re John A. DONOHUE.
Serial No. 263900.
Appeal No. 85-868.

July 3, 1985.

Applicant appealed from a decision of the United States Patent and Trade Mark Office Board of Appeals which sustained final rejection of certain claims of an invention relating to acid compounds which were suitable for producing polymers used to form shaped objects such as film, fibers or molded parts. The Court of Appeals, Jack R. Miller, Senior Circuit Judge, held that the claims were properly rejected as anticipated.

Affirmed.

West Headnotes

[1] **Patents □16(2)**
291k16(2) Most Cited Cases

[1] **Patents □16(3)**
291k16(3) Most Cited Cases
Prior art under 35 U.S.C.A. § 102(b) must sufficiently describe the claimed invention to have placed the public in possession of it; such possession is effected if one of ordinary skill in the art could have combined publication's description of the invention with his own knowledge to make the claimed invention.

[2] **Patents □69**
291k69 Most Cited Cases
Even if claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling; however, it is not necessary that an invention disclosed in a publication actually be made in order to satisfy the enablement requirement. 35 U.S.C.A. § 102(b).

[3] **Courts □96(1)**
106k96(1) Most Cited Cases
Court of Appeals is bound by decisions of the Court of Customs and Patent Appeals.

[4] **Patents □72(1)**
291k72(1) Most Cited Cases
Anticipation rejection requires a showing that each limitation of a claim must be found in a single reference, practice, or device.

[5] **Patents □72(1)**
291k72(1) Most Cited Cases
Claims of an invention relating to acid compounds which were suitable for producing polymers used to form shaped objects, such as film, fibers or molded parts, were properly rejected under 35 U.S.C.A. § 102(b) as anticipated.

Patents □328(2)
291k328(2) Most Cited Cases
3,876,691. Cited.
***531** William Magidson, of Chicago, Ill., argued for appellant.

Harris A. Pitlick, Associate Solicitor, U.S. Patent & Trademark Office, of Arlington, Va., argued for appellee. With him on the brief were Joseph F. Nakamura, Solicitor and John W. Dewhirst, Associate Solicitor, Washington, D.C.

Before MARKEY, Chief Judge, BALDWIN, Circuit Judge, and MILLER, [FN*] Senior Circuit Judge.

FN* Judge Miller assumed senior status effective June 6, 1985.

JACK R. MILLER, Senior Circuit Judge.

This is an appeal from the decision of the U.S. Patent and Trademark Office ("PTO") Board of Appeals ("board") sustaining the ***532** final rejection of appellant's claims [FN1] 1, 2, 5, 6, 7, 25, and 28. We affirm.

FN1. In application Serial No. 263,900, filed May 15, 1981, for Tetramethylbiphenylcarboxylic Acids and Derivatives Thereof, which is a division of Serial No. 60,909, filed July 26, 1979, and a continuation of Serial No. 622,649, filed October 15, 1975, which is a continuation-in-part of Serial No. 517,506, filed October 24, 1974.

BACKGROUND

The subject matter of this appeal was previously

before this court's predecessor in *In re Donohue*, 632 F.2d 123, 207 USPQ 196 (CCPA 1980) ("*Donohue I* "). [FN2] There is no need to discuss the details of that opinion; however, a summary of the pertinent facts is appropriate for a full understanding of the issues before us.

> FN2. *Donohue I* involved application No. 622,649. *See* note 1, *supra*.

The present invention relates to 2,2',6,6'-tetramethylbiphenyl-4,4'- dicarboxylic acid compounds which are suitable for producing polymers used to form shaped objects, such as film, fibers, or molded parts. Claim 1, which is the sole independent claim on appeal, is illustrative:

> 2,2',6,6'-tetramethylbiphenyl-4,4'-dicarboxylic acid compound comprising said acid, an acyl halide derivative thereof, or a simple ester thereof.

The PTO has rejected all the appealed claims under 35 U.S.C. § 102(b) "as anticipated by Nomura [et al.], optionally in view of Lincoln and Walker [et al.]."

Nomura et al. ("Nomura") [FN3] discloses twelve 2,2',6,6'- tetramethylbiphenyls ("TMBP") which are 4,4'-disubstituted with NH_2, NMe_2, OH, OMe, Cl, Br, I, CO_2H, CO_2Me, CN, NO_2, or H substituents. Methods of preparing all these compounds, except those disubstituted with CO_2H or CO_2Me, are set forth in Nomura. Nomura's disclosure of how to make 4,4'- dinitrile (or dicyano) TMBP is particularly significant, because Lincoln [FN4] and Wagner et al. ("Wagner") [FN5] teach, generally, the preparation of carboxylic acids from nitriles by hydrolysis.

> FN3. Yujiro Nomura and Yoshito Takeuchi, "Substituent Effects in Aromatic Proton Nuclear Magnetic Resonance Spectra. Part VI. [$2H_6$] Benzene-induced Solvent Shifts in 4,4'-Disubstituted 2,2',6,6'-Tetramethylbiphenyls and Related Compounds," *J. Chem. Soc'y (B)*, 956-60 (1970).
>
> FN4. U.S. Patent No. 3,876,691, issued April 8, 1975, on application No. 351,696, filed April 16, 1973, for a "Process for the Hydrolysis of Nitriles."
>
> FN5. Wagner et al., *Synthetic Organic Chemistry* 412-15 (John Wiley & Sons, N.Y., N.Y.) (1965).

In *Donohue I*, a majority of the Court of Customs and Patent Appeals ("CCPA") affirmed the PTO's rejection of appealed claims 1, 5, 6, and 7 [FN6] under 35 U.S.C. § 102(b). *Id.* at 127, 207 USPQ at 200. The basis for the rejection was, as it is here, Nomura with reference to Lincoln and Wagner. *Id.* at 126, 207 USPQ at 199.

> FN6. Claim 1 in *Donohue I* differs from claim 1 of the present appeal only in that the latter includes the limitation "comprising said acid, an acyl halide derivative thereof, or a simple ester thereof." Claims 5, 6, and 7 of *Donohue I* specify the same dependent features as in the presently-appealed claims of the same number.

A minority of the CCPA voted to reverse the PTO's decision, because they concluded it was uncertain from the text of Nomura that the dicarboxylic acid TMBP and dimethyl ester TMBP were ever prepared. *Id.* at 129, 207 USPQ at 201. Accordingly, Nomura's disclosure was, in the minority's view, no more than a mere naming of the claimed compounds which is insufficient to constitute an enabling disclosure. *Id.* at 129, 207 USPQ at 201.

After *Donohue I*, the presently-appealed application was filed. During prosecution before the PTO, appellant submitted an affidavit under 37 C.F.R. § 1.132 executed by Dr. Ellis K. Fields ("Fields affidavit"). In this affidavit, Dr. Fields states that he wrote to Dr. Yoshito Takeuchi, one of the authors of Nomura, to ask whether the disclosed dicarboxylic acid TMBP or dimethyl ester TMBP compounds were ever synthesized, as indicated in Nomura. Dr. Takeuchi responded by stating that these compounds were not synthesized, and Dr. ***533** Fields submitted his affidavit to that effect.

Despite the Fields affidavit, the examiner finally rejected the claims, and an appeal to the board was filed. The board affirmed the rejection of the claims on the grounds stated *supra*, holding that it was bound by *Donohue I*. As to the Fields affidavit, the board held that whether the authors of Nomura actually prepared the claimed compounds is not "material or relevant"; rather, the key factor in evaluating the adequacy of a reference's disclosure was deemed to be whether that disclosure would have been enabling, and the board determined that the CCPA had decided that question with respect to Nomura.

ANALYSIS

Appellant has made a record different from that in *Donohue I* by submitting the Fields affidavit. This new record presents a new issue of patentability with respect to whether the previously-sustained anticipation rejection can still be maintained. In view of this new issue, the PTO properly declined to make a formal *res judicata* rejection and addressed the question of whether the Fields affidavit overcomes the rejection of the claims based on Nomura. *See* In re Ackermann, 444 F.2d 1172, 1176, 170 USPQ 340, 343 (CCPA 1971); *In re Russell*, 439 F.2d 1228, 1230, 169 USPQ 426, 428 (CCPA 1971); *In re Herr*, 377 F.2d 610, 611, 153 USPQ 548, 549 (CCPA 1967).

Appellant argues that the Fields affidavit, which states that the authors of Nomura did not make the disclosed dicarboxylic acid TMBP and dimethyl ester TMBP compounds, overcomes the PTO's rejection. It is urged that *Donohue I* and *In re Samour*, 571 F.2d 559, 197 USPQ 1 (CCPA 1978), require, *inter alia*, that a 35 U.S.C. § 102(b) rejection based on a primary reference disclosing a claimed compound in conjunction with one or more references which teach how to make that compound, should be sustained only if the claimed compound was actually made. We disagree.

[1][2] It is well settled that prior art under 35 U.S.C. § 102(v) must sufficiently describe the claimed invention to have placed the public in possession of it. [FN7] *In re Sasse*, 629 F.2d 675, 681, 207 USPQ 107, 111 (CCPA 1980); *In re Samour*, 571 F.2d at 562, 197 USPQ at 4; *see also Reading & Bates Construction Co. v. Baker Energy Resources Corp.*, 748 F.2d 645, 651-52, 223 USPQ 1168, 1173 (Fed.Cir.1984). Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention. *See In re LeGrice*, 301 F.2d at 939, 133 USPQ at 373-74. Accordingly, even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling. *In re Borst*, 345 F.2d 851, 855, 145 USPQ 554, 557 (CCPA 1965), *cert. denied*, 382 U.S. 973, 86 S.Ct. 537, 15 L.Ed.2d 465 (1966). It is not, however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement.

> FN7. This rule is based on the "described in a printed publication" language in 35 U.S.C. § 102(b). *See In re LeGrice*, 301 F.2d 929, 936, 133 USPQ 365, 371 (CCPA 1962).

In re Wiggins, 488 F.2d 538, 179 USPQ 421 (CCPA 1973) and *In re Sheppard*, 339 F.2d 238, 144 USPQ 42 (CCPA 1964), do not support a contrary view. In those cases, the references were deemed insufficient, because they stated that attempts to prepare the claimed compounds were unsuccessful. Such failures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling. By contrast, the fact that the author of a publication did not attempt to make his disclosed invention does not indicate one way or the other whether the publication would have been enabling.

Although *In re Samour* and *Donohue I* mention that the claimed invention in each case was apparently produced in conjunction with the anticipatory reference, this is a far cry from proclaiming that such production ***534** is required to meet the enablement requirement. *In re Samour*, in fact, states:

> [W]hether or not [the claimed invention] has been made previously is not essential to a determination that a method of preparing it would have been known by, or would have been obvious to, one of ordinary skill in the art.

571 F.2d at 563 n. 6, 197 USPQ at 4 n. 6. Therefore, the statements in *In re Samour* and *Donohue I* that the claimed invention was made previously serve to point out the absence of any strong evidence of nonenablement as in *Wiggins* and *Sheppard*. *See In re Donohue*, 632 F.2d at 126 n. 6, 207 USPQ at 199 n. 6.

[3] At oral argument, appellant also challenged the correctness of the CCPA's holding in *In re Samour* and *Donohue I* that several references can be used together to support an anticipation rejection. However, we are bound by the CCPA's decision in those cases. *South Corp. v. United States*, 690 F.2d 1368, 1370-71, 215 USPQ 657, 658 (Fed.Cir.1982) (in banc). At the same time, we have no difficulty with the rejections made in *In re Samour* and *Donohue I*.

[4][5] It is elementary that an anticipation rejection requires a showing that each limitation of a claim must be found in a single reference, practice, or device. *E.g.*, *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 771, 218 USPQ 781, 789 (Fed.Cir.1983), *cert. denied*, 465 U.S. 1026, 104 S.Ct. 1284, 79 L.Ed.2d 687 (1984). The anticipation rejection used here, as in *In re Samour* and *Donohue I*, is not inconsistent with this rule. *See In re Marshall*, 578

F.2d 301, 304, 198 USPQ 344, 346 (CCPA 1978). The additional references utilized in this case (viz., Lincoln and Wagner) are not relied upon for suggestion or motivation to combine teachings to meet the claim limitations, as in rejections under 35 U.S.C. § 103. *In re Samour*, 571 F.2d at 563, 197 USPQ at 4-5. Such reliance would be pointless, because Nomura alone discloses every element claimed. The purpose of citing Lincoln and Wagner is, instead, to show that the claimed subject matter, as disclosed in Nomura, was in the public's possession. *Id.* Therefore, the anticipation rejection based on Nomura, Lincoln, and Wagner is proper. [FN8]

> FN8. *Compare* *Studiengesellschaft Kohle, M.B.H. v. Dart Industries, Inc.*, 726 F.2d 724, 220 USPQ 841 (Fed.Cir.1984) (recognized exception occasionally permitting use of additional references in anticipation rejections but holding exception did not apply).

Appellant also argues that the references fail to teach the solubility characteristics and melting point range set forth in dependent claims 25 and 28, respectively. [FN9] However, where, as here, the dicarboxylic acid TMBP and dimethyl ester TMBP of Nomura are identical to the claimed invention, the properties of Nomura's compounds are inherently the same as those of the claimed invention in the absence of proof to the contrary. *See In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977).

> FN9. Claims 25 and 28 read as follows:
> 25. The acid of Claim 2, said acid being soluble in ether and N-methyl-2-pyrrolidone.
> 28. The dimethyl ester of Claim 7, having a melting point of 128-129° > C.

In view of the foregoing, the board's decision is affirmed.

AFFIRMED

766 F.2d 531, 226 U.S.P.Q. 619

Briefs and Other Related Documents (Back to top)

• 1985 WL 670579 (Appellate Brief) Appellant's Reply Brief (Mar. 29, 1985)Original Image of this Document (PDF)

• 1985 WL 670577 (Appellate Brief) Appellant's Brief (Feb. 01, 1985)Original Image of this Document (PDF)

• 1985 WL 670578 (Appellate Brief) Brief for the Commissioner of Patents and Trademarks (1985)Original Image of this Document (PDF)

END OF DOCUMENT

C

In re Bundy

Court of Customs and Patent Appeals

No. 80-591

Decided Feb. 26, 1981
United States Patents Quarterly Headnotes

PATENTS
[1] Patentability -- Utility (§ 51.75)
Pleading and practice in courts -- Burden of proof -- In general (§ 53.131)
Pleading and practice in Patent Office -- Rejections (§ 54.7)
Specification -- Sufficiency of disclosure (§ 62.7)
Burden shifts to appellant to provide rebuttal evidence, where enablement question is whether disclosure of utility in terms of being useful and used in same manner as known series of analogs of prostaglandins is sufficient to satisfy how-to-use requirement of first paragraph of 35 U.S.C. 112, only when Patent Office has adequate support for its challenge to credibility of applicant's statements as to utility.

PATENTS
[2] Specification -- Sufficiency of disclosure (§ 62.7)
Disclosure of some activity coupled with knowledge as to use of this activity is necessary to satisfy how-to-use requirement of Section 112.

PATENTS
[3] Specification -- Sufficiency of disclosure (§ 62.7)
Situation in which sufficient guidelines as to use are given in disclosure is not same situation as in In re Gardner, 166 USPQ 138; no parallel can be drawn to In re Kirk, 153 USPQ 48, where in present case basic pharmacological activity has been established and not merely presumed from similar molecular structure.

PATENTS
[4] Patent grant -- Intent of patent laws (§ 50.15)
Specification -- Sufficiency of disclosure (§ 62.7)
Early filing of application with its disclosure of novel compounds that possess significant therapeutic use is to be encouraged; requiring specific testing of thousands of prostaglandin analogs encompassed by claim in order to satisfy how-to-use requirement of Section 112 would delay disclosure and frustrate, rather than further, interests of public.

PATENTS
[5] Pleading and practice in Patent Office -- Rejections (§ 54.7)
Specification -- Sufficiency of disclosure (§ 62.7)
Although holding that appellant has adequately told how to use novel compounds necessarily undercuts best mode rejection founded on lack of enablement, thrust of inquiry is not same for determining satisfaction of further requirement that specification set forth best mode contemplated by inventor for carrying out his invention; satisfaction of best mode requirement of Section 112 is question separate and distinct from question of sufficiency of disclosure to comply with enablement provision; question is one of concealment, i.e., whether applicant has withheld what he considers to be best mode of carrying out his invention; best mode requirement does not require one to obtain further knowledge but only to disclose what one knows or, at least, contemplates.

PATENTS
[6] Specification -- Sufficiency of disclosure (§ 62.7)
Inference of withholding of information as to best mode of use cannot be made from appellant's general statements of increased selectivity and narrower spectrum of potency of novel analogs that are conclusions that could be drawn from elementary pharmacological testing of prostaglandin analogs that established basic E-type activity.

PATENTS
Particular patents -- Prostaglandins
Bundy, 3,7-Inter-m-Phenylene-4,5,6-Trinor-2-Decarboxy-2-Hydroxymethyl-9 - Deoxy-9-Methylene-PGF-Type Compounds, rejection of sole claim reversed.

***48** Appeal from Patent and Trademark Office Board of Appeals.

Application for patent of Gordon L. Bundy, Serial No. 832,329, filed Sept. 12, 1977, division of application, Serial No. 682,848, filed May 4, 1976, issued as U.S. patent No. 4,060,530, Nov. 29, 1977. From rejection of sole claim, applicant appeals. Reversed.

Robert A. Armitage, Kalamazoo, Mich., for appellant.

Joseph F. Nakamura (Gerald H. Bjorge, of counsel) for Patent and Trademark Office.

Before Markey, Chief Judge, and Rich, Baldwin, Miller, and Nies, Associate Judges.

***49** Nies, Judge.

This appeal is from the decision of the Patent and Trademark Office (PTO) Board of Appeals (board) affirming the rejection of the sole claim of appellant's application [FN1] under the first paragraph of 35 USC 112. [FN2] We reverse.

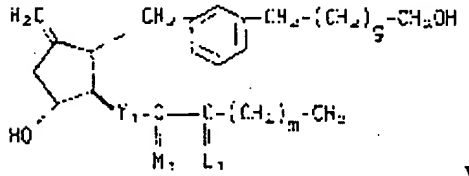
The appeal raises questions regarding the extent to which new pharmaceuticals must be tested, preceding the filing of an application, in order to satisfy the how-to-use and best mode requirements of § 112.

The Invention

The invention relates to a new series of analogs of naturally-occurring prostaglandins [FN3] which differ from the corresponding known prostaglandins in that these analogs have a methylene group at the C-9 position [FN4]. Structurally, the compounds may be considered analogs of either E-type prostaglandins (PGEs) in which the methylene group replaces the usual C-9 keto-or oxo-group or of F-type prostaglandins (PGFs) in which the methylene group replaces the C-9 hydroxyl group. Pharmacologically, however, the analogs are related only to PGEs.

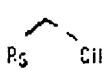
The sole claim reads:

131. A prostaglandin analog of the formula

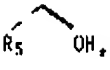


wherein Ysub1 is trans --CH=CH--, --C=C--, or --CHsub2 CHsub2 ;

wherein Msub1 is



or



wherein Rsub5 is hydrogen or methyl;

wherein Lsub1 is

or a mixture of

and

wherein Rsub3 and Rsub4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of Rsub3 and Rsub4 is fluoro only when the other is hydrogen or fluoro;

wherein g is one, 2 or 3; and

wherein m is one to 5, inclusive.

The Disclosure

The specification of U.S. Patent No. 4,060,534 ('534) has been incorporated by reference to serve as the specification for the present application. The portions of the specification directed to using these novel analogs are pertinent to the issues on appeal.

The background section of the specification contains a detailed description of the uses of various *known* PGEsubs . Nine specific biological responses caused by PGEsubs , ranging from decreasing blood pressure to inhibiting gastric secretion, are listed. Based on these responses, various pharmacological uses with broad ranges of dosage by various methods of administration are enumerated.

***50** The use of appellant's novel analogs, which include not only the claimed compounds of this application, but also those claimed in other divisional applications and in '534, is subsequently set forth:

> The novel prostaglandin analogs of this invention correspond to the prostaglandins described above in that the novel prostaglandin analogs exhibit prostaglandin-like activity.
>
> Specifically the 9-deoxy-9-methylene-PGF-type compounds of this invention correspond to the PGE compounds described above, in that these novel 9-deoxy-9-methylene-PGF-type compounds are useful for each of the above-

> described purposes for which the PGE compounds are used, and are used in the same manner as the PGE compounds, as described above.
>
> The PGE compounds described above, are all potent in causing multiple biological responses even at low doses. Moreover, for many applications, these prostaglandins have an inconveniently short duration of biological activity. In striking contrast, the novel prostaglandin analogs of this invention are substantially more selective with regard to potency in causing prostaglandin-like biological responses, and have a substantially longer duration of biological activity. Accordingly, each of these novel prostaglandin analogs is surprisingly and unexpectedly more useful than one of the corresponding prostaglandins described above for at least one of the pharmacological purposes indicated above for the latter, because it has a different and narrower spectrum of biological potency than the known prostaglandin, and therefore is more specific in its activity and causes smaller and fewer undesired side effects than when the prostaglandin is used for the same purpose. Moreover, because of its prolonged activity, fewer and smaller doses of the novel prostaglandin analog are frequently effective in attaining the desired result.

The specification includes a disclosure relating to preparation of the compounds generally, and several specific examples. None, however, are compounds within the subgenus claimed in this application.

No example of a specific use of *any* of the disclosed prostaglandin analogs, i.e., setting forth a dosage to achieve a desired response, is given.

The Rejection

The examiner rejected the sole claim under the first paragraph of 35 USC 112 as being "inadequately supported by the instant specification" in that not a single example was directed to one of the claimed compounds. Failure to meet the best mode requirement was also raised on the basis of no exemplification. Reliance on utilities similar to known PGEsubs was attacked on the basis of a statement in a "Samuelsson et al. reference" (more correctly, a Rosenthale paper therein) [FN5] that "small changes in the [prostaglandin] molecule can alter potency or even induce diametrically opposite pharmacologic effects." Thus, the utilities asserted on the basis of those known for structurally analogous compounds were said to be "at best highly speculative."

Before the board the § 112 rejection was more specifically explained by the examiner to encompass an inadequate disclosure of: (1) the description of the compounds; (2) the preparation of the same; (3) their use; and (4) the best mode of carrying out the invention. The examiner added that an undue amount of experimentation would be required to prepare the claimed compounds and to determine their utilities.

The board held that the description and how-to-make requirements of the first paragraph of 35 USC 112 were satisfied by appellant's disclosure. It agreed with the examiner, however, that:

> [U]ndue experimentation would be required on the part of one of ordinary skill in the relevant art to determine how to use the compounds claimed. Since we consider the manner of using a compound to be necessarily a part of "the best mode contemplated by the inventor of carrying out the invention", we also agree with the examiner's position that the best mode requirement has not been met.

The challenge raised by the examiner's citation of the Rosenthale paper was deemed reasonable and unrebutted by any factual evidence. The board then added:

> [O]ne of the advantages alleged for the compounds here claimed is that they are more selective than the analogous PGE compounds. This is an express indication ***51** that not all of the compounds covered by appellant's claims will induce the same biological responses.

Accordingly, the board affirmed the examiner's rejection of the sole claim to the extent it was based on the how-to-use and best mode requirements of § 112.

Opinion

How-to-Use

The enablement question present here is whether the disclosure of utility in terms of being useful and used in the same manner as known PGEs is sufficient to satisfy the how-to-use requirement of the first paragraph of 35 USC 112.

[1] The PTO must have adequate support for its

challenge to the credibility of applicant's statements as to utility. Only then does the burden shift to appellant to provide rebuttal evidence. In re Gardner, 475 F.2d 1389, 177 USPQ 396 (CCPA 1973); In re Marzocchi, 58 CCPA 1069, 439 F.2d 220, 169 USPQ 367 (1971). We must consider the Rosenthale paper in its entirety in determining the reasonableness of the doubt raised by the authors' conclusory statement relied on by the examiner, and in so doing see no specific evidence that structural variations of PGEs cause opposite pharmacologic effects. The tests reported by Rosenthale do indicate shifts in PGFsub2a activity from bronchoconstrictor to broncodilator concomitant with structural changes. For PGE Rosenthale shows only variations in potency, a matter of degree of activity. Accordingly, we do not agree that Rosenthale is sufficient support for the examiner's position that the subject analogs, related as they are to PGEsubs in pharmacological activity, may not be useful at all to achieve a particular response.

The board focused on another reason for challenging the disclosure as non-enabling. Appellant's disclosure of increased "selectivity" of the novel analogs was taken as an express indication that it was uncertain "which compound will induce which biological responses * * *," thus virtually ensuring that an undue amount of experimentation would be required to use the invention. The ranges of dosage for known PGEs, assuming their applicability to appellant's analogs, were said to be very broad and would, in any event, provide little guidance in determining dosages for the more selectively functional claimed analogs.

Appellant contends that the disclosure teaches that *all* novel compounds exhibit *each* of the enumerated pharmacological uses. The increased selectivity is said to be with respect to the potency for each activity, not to the existence of that biological activity. Any contrary interpretation of the specification is strongly denied. As far as determining dosages for the novel analogs is concerned, it is urged that the experimentation needed to ascertain proper levels for various responses would not be undue, but rather would lie well within the ability of one of ordinary skill in the art. At most, appellant states, the question is whether the determinations would be extended, not undue.

[2] We have no difficulty with appellant's interpretation of "selectivity". In the pertinent section, previously quoted, it is clearly stated that the novel compounds are "useful for *each* of the above-described purposes for which the PGE compounds are used" (emphasis added). This can only reasonably be read as teaching that *each* compound can be used for *each* and every one of the aforesaid biological responses. Appellant's further statements that the novel analogs are "substantially more selective with regard to potency" or "more specific in its activity" because of a "different and narrower spectrum of biological potency," does not negate the asserted usefulness for each purpose. There is no requirement that all have the same degree of activity for each use. What is necessary to satisfy the how-to-use requirement of § 112 is the disclosure of some activity coupled with knowledge as to the use of this activity. In re Gardner, 475 F.2d at 1392, 177 USPQ at 398.

Thus the remaining question is whether appellant's disclosure is sufficient to enable one of ordinary skill in the art to use these novel analogs. No specific examples of dosages for human use or even animal tests are given for the novel compounds per se. Appellant's counsel stated at oral argument that all that had been established at the time of filing the application was the basic pharmacology for these compounds. Appellant's specification discloses that these compounds possess activity similar to E-type prostaglandins. As to the latter, dosages are disclosed, albeit expressed in very broad ranges.

[3] We do not consider that one of ordinary skill in the art would not know how to use these novel analogs to determine the specific dosages for the various biological purposes. We are persuaded that sufficient guidelines as to use are given in the disclosure here. This is not the same situation as in In re Gardner et al., 57 CCPA 1207, 427 F.2d 786, 166 USPQ 138 (1970). Here ***52** only the compounds themselves are being claimed, not their therapeutic use. Nor can a parallel be drawn to In re Kirk, 54 CCPA 1119, 376 F.2d 936, 153 USPQ 48 (1967), the basic pharmacological activity having been established in this case, not merely *presumed* from similar molecular structure.

[4] Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of § 112 would delay disclosure and frustrate, rather than further, the interests of the public.

Accordingly, we are satisfied that the how-to-use requirement of the first paragraph of § 112 has been adequately complied with by appellant's disclosures.

Best Mode

[5] Turning to the best mode issue, we agree with appellant that this rejection was founded on a lack of enablement by both the examiner and the board. Our holding that appellant has adequately told how to use the novel compounds necessarily undercuts this position. However, we do not agree that the thrust of the inquiry is the same for determining satisfaction of the further requirement that the specification shall set forth the best mode contemplated by the inventor of carrying out his invention.

Satisfaction of the best mode requirement of § 112 is a question separate and distinct from the question of the sufficiency of the disclosure to comply with the enablement provision. In re Gay, 50 CCPA 725, 731, 309 F.2d 769, 772, 135 USPQ 311, 315 (1962). The question is one of concealment, i.e., whether an applicant has *withheld* what he considers to be the best mode of carrying out his invention. The best mode requirement does not require one to obtain further knowledge but only to disclose what one knows or, at least, contemplates.

The Solicitor argued that concealment may be inferred. Quoting the disclosure in the specification that each analog is "surprisingly and unexpectedly more useful than one of the corresponding prostaglandins * * * for at least one of the pharmacological purposes * * *," he urges that appellant must have had test results to substantiate this statement and this data should have been disclosed. The alleged withholding of information on which these general statements were made is said to render the quality of disclosure so poor that it effectively results in concealment, citing In re Sherwood, 613 F.2d 809, 816, 204 USPQ 537, 544 (CCPA 1980).

[6] Were we to see merit in the Solicitor's position fairness would require providing appellant with the opportunity to present evidence in rebuttal. However, we do not find it necessary for appellant to assume this burden of proof. We can infer no withholding of information as to the best mode of use from appellant's general statements of increased selectivity and narrower spectrum of potency for these novel analogs, conclusions which could be drawn from the elementary pharmacological testing of the analogs which established the basic E-type activity.

Accordingly, we reverse the holding that the best mode requirement has not been satisfied.

Conclusion

The board's affirmance of the rejection of appellant's sole claim under both the how-to-use and the best mode requirements of the first paragraph of § 112 is *reversed.*

Reversed.

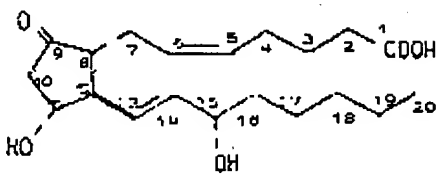
FN1 Serial No. 832,329, filed September 12 1977, for 3, 7-Inter-m-Phenylene-4, 5, 6-Trinor-2-Decarboxy-2-Hydroxymethyl- 9 - Deoxy-9-Methylene-PGF-Type Compounds. The application is a divisional application of Ser. No. 682,848, filed May 4, 1976, issued as U.S. Patent No. 4,060,534 on November 29, 1977.

FN2 The first paragraph of § 112 reads:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

FN3 Natural prostaglandins are found in mammalian tissues and have varied pharmacologic uses including the treatment of hypertension, ulcers and asthma, and the interruption of pregnancy. In naming the prostaglandins, the prefix PG is followed by a letter designating the oxidation state of the cyclopentane ring; thus arise the series PGA, PGE, PGF, etc. The numeral subscript refers to the number of double bonds in the side chain. 1 D. Lednicer & L. Mitscher, The Organic Chemistry of Drug Synthesis, 23-27 (1977).

FN4 A typical example of a naturally-occurring prostaglandin is PGEsub2 which structurally is represented:



FN

5 Cited by the examiner as: Samuelsson et al., Advances in Prostaglandin and Thromboxane Research, Vol. 1 (1976) 488-491.Appellant has pointed out that the work relied upon is a paper by Rosenthale et al. entitled "Actions of Prostaglandins on the Respiratory Tract of Animals," pp. 477-493 included in the above book, edited by Samuelsson et al. Henceforth we shall refer to this reference as the Rosenthale paper.

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209 U.S.P.Q. 48

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C

United States Court of Appeals,
Federal Circuit.
In re Miguel F. BRANA, Jose M.C. Berlanga, Marina M. Moset, Erich Schlick and Gerhard Keilhauer.
93-1393.

March 30, 1995.

Applicants appealed from decision of the United States Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences, affirming patent examiner's rejections of claims for antitumor compound. The Court of Appeals, Plager, Circuit Judge, held that: (1) claimed specification for antitumor compound satisfied statutory utility requirement by alleging that compound was more effective in treating lymphocytic leukemia in mice than other known compounds; (2) PTO failed to satisfy its initial burden of challenging presumptively correct assertion of utility; (3) even if one skilled in the art would have reasonably questioned asserted utility of claimed antitumor compound, applicants provided sufficient evidence to convince one of skill in the art of asserted utility; and (4) Food and Drug Administration (FDA) approval is not prerequisite for finding compound useful within meaning of patent laws.

Reversed.

West Headnotes

[1] Patents 101(5)
291k101(5) Most Cited Cases
Claim specifications for antitumor compound satisfied statutory utility requirement by alleging that compound was more effective in treating lymphocytic leukemia in mice than other known compounds. 35 U.S.C.A. § 101.

[2] Patents 48
291k48 Most Cited Cases
Lymphocytic leukemia tumor models used to study cancer in mice represented specific diseases against which claimed compounds in patent application could be effective, as required to satisfy statutory utility requirement, where cell lines used on models were originally derived from lymphocytic leukemias in mice and would produce that disease once implanted in mice. 35 U.S.C.A. § 101.

[3] Patents 97
291k97 Most Cited Cases
Patent and Trademark Office (PTO) has initial burden of challenging presumptively correct assertion of utility in patent disclosure. 35 U.S.C.A. § 101.

[4] Patents 97
291k97 Most Cited Cases
Only after Patent and Trademark Office (PTO) provides evidence showing that one of ordinary skill in art would reasonably doubt asserted utility of patented invention does burden shift to applicant to provide rebuttal evidence sufficient to convince such person of invention's asserted utility. 35 U.S.C.A. § 101.

[5] Patents 97
291k97 Most Cited Cases
Patent and Trademark Office (PTO) failed to satisfy its initial burden of challenging presumptively correct assertion of utility in application for patent for antitumor compound, where references cited by PTO did not question usefulness of any compound as antitumor agent or provide any other evidence to cause one of skill in the art to question asserted utility of applicants' compounds, but instead discussed therapeutic predictive value of tests used in mice, which were relevant only if applicants were required to prove ultimate value in humans of their asserted utility. 35 U.S.C.A. § 101.

[6] Patents 99
291k99 Most Cited Cases
Even if one skilled in the art would have reasonably questioned asserted utility of claimed antitumor compound, applicants provided sufficient evidence to convince one of skill in the art of asserted utility; applicants provided test results showing that several compounds within scope of claims exhibited significant antitumor activity, and prior art disclosed structurally similar compounds which were proven to be effective antitumor agents. 35 U.S.C.A. § 101.

[7] Patents 49
291k49 Most Cited Cases
Although minor changes in chemical compounds can radically change their effects on human body, evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe asserted utility.

[8] Patents 46
291k46 Most Cited Cases
Food and Drug Administration (FDA) approval is not prerequisite for finding compound useful within

meaning of patent laws. Federal Food, Drug, and Cosmetic Act, § 505(i)(1), 21 U.S.C.A. § 355(i)(1); 35 U.S.C.A. § § 101, 112; 21 C.F.R. § § 312.21(b), 312.23(a)(5), (a)(8).

[9] Patents 324.5
291k324.5 Most Cited Cases
In reviewing decisions of Patent and Trademark Office (PTO), Court of Appeals traditionally reviews questions of law without deference to views of the agency, and defers to agency with regard to questions of fact unless its findings are clearly erroneous.

[10] Patents 324.55(1)
291k324.55(1) Most Cited Cases
When mixed questions of law and fact are before Court of Appeals on appeal from decision of Patent and Trademark Office (PTO), whether Court of Appeals defers, and extent to which it defers to agency's decision, turns on nature of case and nature of judgment. 5 U.S.C.A. § 706.

***1562** Malcolm J. MacDonald, Keil & Weinkauf, Washington, DC, argued, for appellant. With him on the brief was Herbert B. Keil. Of counsel was David S. Nagy.

Fred E. McKelvey, Sol., Office of Sol., Arlington, VA, argued, for appellee. With him on the brief were Albin F. Drost, Deputy Sol., Richard E. Schafer, Teddy S. Gron, Joseph G. Piccolo and Richard L. Torczon, Associate Sols.

Before PLAGER, LOURIE, and RADER, Circuit Judges.

PLAGER, Circuit Judge.

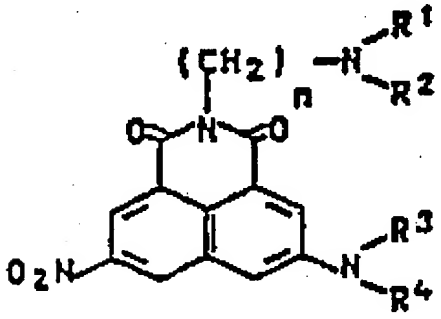
Miguel F. Brana, *et al.* (applicants), appeal the March 19, 1993 decision of the United States Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), in Appeal No. 92-1196. The Board affirmed the examiner's rejection of claims 10-13 of patent application Serial No. 533,944 under 35 U.S.C. § 112 ¶ 1 (1988). [FN1] The examiner's rejection, upon which the Board relied in rendering its decision, was based specifically on a challenge to the utility of the claimed compounds and the amount of experimentation necessary to use the compounds. We conclude the Board erred, and reverse.

FN1. Unless otherwise noted, all United States Code citations are to the 1988 edition.

I. BACKGROUND

On June 30, 1988, applicants filed patent application Serial No. 213,690 (the '690 application) [FN2] directed to 5-nitrobenzo[de]isoquinoline-1,3- dione compounds, for use as antitumor substances, having the following formula:

FN2. This is a divisional of patent application Serial No. 110,871 filed October 21, 1987.



where n is 1 or 2, R1 and R2 are identical or different and are each hydrogen, C_1-C_6-alkyl, C_1-C_6-hydroxyalkyl, pyrrolidinyl, morpholino, piperidinyl or piperacinyl, and R3 and R4 are identical or different and are each hydrogen, C_1-C_6-alkyl, C_1-C_6-acyl, C_2-C_7-alkoxycarbonyl, ureyl, aminocarbonyl or C_2-C_7-alkylaminocarbonyl. These claimed compounds differ from several prior art benzo[de]isoquinoline-1,3-dione compounds due to the presence of a nitro group (O_2N) at the 5-position and an amino or other amino group (NR3R4) at the 8-position of the isoquinoline ring.

The specification states that these non-symmetrical substitutions at the 5-and 8-positions produce compounds with "a better action and a better action spectrum as antitumor substances" than known benzo[de]isoquinolines, namely those in K.D. Paull et al., *Computer Assisted Structure-Activity Correlations,* Drug Research, 34(II), 1243-46 (1984) (Paull). Paull describes a computer-assisted evaluation of benzo[de]isoquinoline-1,3-diones and related compounds which have been screened for antitumor activity by testing their efficacy ***in vivo*** [FN3] against two specific implanted murine (i.e., utilizing mice as test subjects) lymphocytic leukemias, P388 and L1210. [FN4] These two ***in vivo*** tests are ***1563** widely used by the National Cancer Institute (NCI) to measure the antitumor properties of a compound. Paull noted that one compound in particular, benzo[de]isoquinoline-1,3(2H)dione,5-amino-2(2-dimethyl-aminoethyl [sic]) (hereinafter "NSC 308847"), was found to show excellent activity against these two specific tumor

models. Based on their analysis, compound NSC 308847 was selected for further studies by NCI. In addition to comparing the effectiveness of the claimed compounds with structurally similar compounds in Paull, applicants' patent specification illustrates the cytotoxicity of the claimed compounds against human tumor cells, ***in vitro,*** [FN5] and concludes that these tests "had a good action." [FN6]

FN3. ***In vivo*** means "[i]n the living body, referring to a process occurring therein." Steadman's Medical Dictionary 798 (25th ed. 1990). ***In vitro*** means "[i]n an artificial environment, referring to a process or reaction occurring therein, as in a test tube or culture media." *Id.*

FN4. The analysis in Paull consisted of grouping the previously-tested compounds into groups based on common structural features and cross-referencing the various groups, in light of the success rates of the group as a whole, to determine specific compounds that may be effective in treating tumors.

FN5. *See supra* note 3.

FN6. The specification does not state the specific type of human tumor cells used in this test.

The examiner initially rejected applicants' claims in the '690 application as obvious under 35 U.S.C. § 103 in light of U.S. Patent No. 4,614,820, issued to and referred to hereafter as Zee-Cheng et al. Zee-Cheng et al. discloses a benzo[de]isoquinoline compound for use as an antitumor agent with symmetrical substitutions on the 5-position and 8-position of the quinoline ring; in both positions the substitution was either an amino or nitro group. [FN7] Although not identical to the applicants' claimed compounds, the examiner noted the similar substitution pattern (i.e., at the same positions on the isoquinoline ring) and concluded that a mixed substitution of the invention therefore would have been obvious in view of Zee-Cheng et al.

FN7. The chemical compound in Zee-Cheng et al. is labeled a 3,6- disubstituted-1,8-naphthalimide and uses different numbering for the positions on the isoquinoline ring. The structure of this compound, however, is identical to that claimed by the applicants except for symmetrical substitutions at the 5-position and the 8-position of the isoquinoline ring. Zee-Cheng et al. teaches identical substitutions of amino or nitro groups while applicants claim a nitro group substitution at the 5-position and an amino group substitution at the 8-position.

In a response dated July 14, 1989, the applicants rebutted the § 103 rejection. Applicants asserted that their mixed disubstituted compounds had unexpectedly better antitumor properties than the symmetrically substituted compounds in Zee-Cheng et al. In support of this assertion applicants attached the declaration of Dr. Gerhard Keilhauer. In his declaration Dr. Keilhauer reported that his tests indicated that applicants' claimed compounds were far more effective as antitumor agents than the compounds disclosed in Zee-Cheng et al. when tested, ***in vitro,*** against two specific types of human tumor cells, HEp and HCT-29. [FN8] Applicants further noted that, although the differences between the compounds in Zee-Cheng et al. and applicants' claimed compounds were slight, there was no suggestion in the art that these improved results (over Zee-Cheng et al.) would have been expected. Although the applicants overcame the § 103 rejection, the examiner nevertheless issued a final rejection, on different grounds, on September 5, 1989.

FN8. HEp cells are derived from laryngeal cancer and HCT-29 cells from colon cancer.

On June 4, 1990, applicants filed a continuation application, Serial No. 533,944 (the '944 application), from the above-mentioned '690 application. Claims 10-13, the only claims remaining in the continuation application, were rejected in a final office action dated May 1, 1991. Applicants appealed the examiner's final rejection to the Board.

In his answer to the applicants' appeal brief, the examiner stated that the final rejection was based on 35 U.S.C. § 112 ¶ 1. [FN9] The examiner first noted that the specification failed to describe any specific disease against which the claimed compounds were active. Furthermore, the examiner concluded that the prior art tests performed in Paull and the tests disclosed in the specification were not sufficient to establish a reasonable expectation that the claimed compounds had ***1564** a practical utility (i.e. antitumor activity in humans). [FN10]

FN9. The examiner's answer noted that the final rejection also could have been made

under 35 U.S.C. § 101 for failure to disclose a practical utility.

FN10. The examiner subsequently filed two supplemental answers in response to arguments raised by the applicants in supplemental reply briefs.

In a decision dated March 19, 1993, the Board affirmed the examiner's final rejection. The three-page opinion, which lacked any additional analysis, relied entirely on the examiner's reasoning. Although noting that it also would have been proper for the examiner to reject the claims under 35 U.S.C. § 101, the Board affirmed solely on the basis of the Examiner's § 112 ¶ 1 rejection. This appeal followed.

II. DISCUSSION

At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant prove regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago. [FN11] We note the Commissioner has recently addressed this question in his Examiner Guidelines for Biotech Applications, *see* 60 Fed.Reg. 97 (1995); 49 Pat.Trademark & Copyright J. (BNA) No. 1210, at 234 (Jan. 5, 1995).

FN11. *See, e.g., Cross v. Iizuka,* 753 F.2d 1040, 224 USPQ 739 (Fed.Cir.1985); *In re Langer,* 503 F.2d 1380, 183 USPQ 288 (CCPA 1974); *In re Krimmel,* 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *In re Bergel,* 292 F.2d 958, 130 USPQ 205 (CCPA 1961).

The requirement that an invention have utility is found in 35 U.S.C. § 101: "Whoever invents ... any new and *useful* ... composition of matter ... may obtain a patent therefor...." (emphasis added). It is also implicit in § 112 ¶ 1, which reads:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it.

As noted, although the examiner and the Board both mentioned § 101, and the rejection appears to be based on the issue of whether the compounds had a practical utility, a § 101 issue, the rejection according to the Board stands on the requirements of § 112 ¶ 1. It is to that provision that we address ourselves. [FN12] The Board gives two reasons for the rejection; [FN13] we will consider these in turn.

FN12. This court's predecessor has determined that absence of utility can be the basis of a rejection under both 35 U.S.C. § 101 and § 112 ¶ 1. *In re Jolles,* 628 F.2d 1322, 1326 n. 11, 206 USPQ 885, 889 n. 11 (CCPA 1980); *In re Fouche,* 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971) ("[I]f such compositions are in fact useless, appellant's specification cannot have taught how to use them."). Since the Board affirmed the examiner's rejection based solely on § 112 ¶ 1, however, our review is limited only to whether the application complies with § 112 ¶ 1.

FN13. The Board's decision did not expressly make any independent factual determinations or legal conclusions. Rather, the Board stated that it "agree[d] with the examiner's well reasoned, well stated and fully supported by citation of relevant precedent position in every particular, and any further comment which we might add would be redundant." *Ex parte Brana et al.,* No. 92-1196 (Bd.Pat.App. & Int. March 19, 1993) at 2- 3. Therefore, reference in this opinion to Board findings are actually arguments made by the examiner which have been expressly adopted by the Board.

1.

[1] The first basis for the Board's decision was that the applicants' specification failed to disclose a specific disease against which the claimed compounds are useful, and therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed.Cir.1986), *cert. denied,* 480 U.S. 947, 107 S.Ct. 1606, 94 L.Ed.2d 792 (1987). In support, the Commissioner argues that the disclosed uses in ***1565** the '944 application,

namely the "treatment of diseases" and "antitumor substances," are similar to the nebulous disclosure found insufficient in *In re Kirk*, 376 F.2d 936, 153 USPQ 48 (CCPA 1967). This argument is not without merit.

In *Kirk* applicants claimed a new class of steroid compounds. One of the alleged utilities disclosed in the specification was that these compounds possessed "high biological activity." *Id.* at 938, 153 USPQ at 50. The specification, however, failed to disclose which biological properties made the compounds useful. Moreover, the court found that known specific uses of similar compounds did not cure this defect since there was no disclosure in the specification that the properties of the claimed compounds were the same as those of the known similar compounds. *Id.* at 942, 153 USPQ at 53. Furthermore, it was not alleged that one of skill in the art would have known of any specific uses, and therefore, the court concluded this alleged use was too obscure to enable one of skill in the art to use the claimed invention. *See also Kawai v. Metlesics*, 480 F.2d 880, 178 USPQ 158 (CCPA 1973).

Kirk would potentially be dispositive of this case were the above-mentioned language the only assertion of utility found in the '944 application. Applicants' specification, however, also states that the claimed compounds have "a better action and a better action spectrum as antitumor substances" than known compounds, specifically those analyzed in Paull. As previously noted, *see supra* note 4, Paull grouped various benzo[de]isoquinoline-1,3- diones, which had previously been tested *in vivo* for antitumor activity against two lymphocytic leukemia tumor models (P388 and L1210), into various structural classifications and analyzed the test results of the groups (i.e. what percent of the compounds in the particular group showed success against the tumor models). Since one of the tested compounds, NSC 308847, was found to be highly effective against these two lymphocytic leukemia tumor models, [FN14] applicants' favorable comparison implicitly asserts that their claimed compounds are highly effective (i.e. useful) against lymphocytic leukemia. An alleged use against this particular type of cancer is much more specific than the vaguely intimated uses rejected by the courts in *Kirk* and *Kawai*. *See, e.g., Cross v. Iizuka*, 753 F.2d at 1048, 224 USPQ at 745 (finding the disclosed practical utility for the claimed compounds--the inhibition of thromboxane synthetase in human or bovine platelet microsomes--sufficiently specific to satisfy the threshold requirement in *Kirk* and *Kawai*.)

FN14. Paull also found NSC 308847 to be effective against two other test models, B16 melanoma and Colon C872.

[2] The Commissioner contends, however, that P388 and L1210 are not diseases since the only way an animal can get sick from P388 is by a direct injection of the cell line. The Commissioner therefore concludes that applicants' reference to Paull in their specification does not provide a specific disease against which the claimed compounds can be used. We disagree.

As applicants point out, the P388 and L1210 cell lines, though technically labeled tumor models, were originally derived from lymphocytic leukemias in mice. Therefore, the P388 and L1210 cell lines do represent actual specific lymphocytic tumors; these models will produce this particular disease once implanted in mice. If applicants were required to wait until an animal naturally developed this specific tumor before testing the effectiveness of a compound against the tumor ***in vivo***, as would be implied from the Commissioner's argument, there would be no effective way to test compounds ***in vivo*** on a large scale.

We conclude that these tumor models represent a specific disease against which the claimed compounds are alleged to be effective. Accordingly, in light of the explicit reference to Paull, applicants' specification alleges a sufficiently specific use.

2.

[3][4] The second basis for the Board's rejection was that, even if the specification did allege a specific use, applicants failed to ***1566** prove that the claimed compounds are useful. Citing various references, [FN15] the Board found, and the Commissioner now argues, that the tests offered by the applicants to prove utility were inadequate to convince one of ordinary skill in the art that the claimed compounds are useful as antitumor agents. [FN16]

FN15. *See* Pazdur et al., *Correlation of Murine Antitumor Models in Predicting Clinical Drug Activity in Non-Small Cell Lung Cancer: A Six Year Experience*, 3 Proceedings Am.Soc.Clin.Oncology 219 (1984); Martin et al., *Role of Murine Tumor Models in Cancer Research*, 46 Cancer Research 2189 (April 1986).

FN16. As noted, this would appear to be a §

101 issue, rather than § 112.

This court's predecessor has stated:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. *Id.* at 224, 169 USPQ at 370. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *See In re Bundy*, 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981). [FN17]

FN17. *See also In re Novak*, 306 F.2d 924, 928, 134 USPQ 335, 337 (CCPA 1962) (stating that it is proper for the examiner to request evidence to substantiate an asserted utility unless one with ordinary skill in the art would accept the allegations as obviously valid and correct); *In re Chilowsky*, 229 F.2d 457, 462, 108 USPQ 321, 325 (CCPA 1956) ("[W]here the mode of operation alleged can be readily understood and conforms to the known laws of physics and chemistry ... no further evidence is required."). *But see In re Marzocchi*, 439 F.2d at 223, 169 USPQ at 369-70 ("In the field of chemistry generally there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles.").

[5] The PTO has not met this initial burden. The references cited by the Board, Pazdur and Martin, [FN18] do not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, these references merely discuss the therapeutic predictive value of *in vivo* murine tests--relevant only if applicants must prove the ultimate value in humans of their asserted utility. Likewise, we do not find that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness.

FN18. *See supra* note 15.

The purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. *In re Jolles*, 628 F.2d at 1327, 206 USPQ at 890. Modern science has previously identified numerous successful chemotherapeutic agents. In addition, the prior art, specifically Zee Cheng et al., discloses structurally similar compounds to those claimed by the applicants which have been proven *in vivo* to be effective as chemotherapeutic agents against various tumor models.

Taking these facts--the nature of the invention and the PTO's proffered evidence--into consideration we conclude that one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face. The PTO thus has not satisfied its initial burden. Accordingly, applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of § 112. *See In re Marzocchi*, 439 F.2d at 224, 169 USPQ at 370.

[6] We do not rest our decision there, however. Even if one skilled in the art ***1567** would have reasonably questioned the asserted utility, i.e., even if the PTO met its initial burden thereby shifting the burden to the applicants to offer rebuttal evidence, applicants proffered sufficient evidence to convince one of skill in the art of the asserted utility. In particular, applicants provided through Dr. Kluge's declaration [FN19] test results showing that several compounds within the scope of the claims exhibited significant antitumor activity against the L1210 standard tumor model ***in vivo.*** Such evidence alone should have been sufficient to satisfy applicants' burden.

FN19. The declaration of Michael Kluge was signed and dated June 19, 1991. This declaration listed test results (i.e. antitumor activity) of the claimed compounds, *in vivo,* against L1210 tumor cells and concluded

> that these compounds would likely be clinically useful as anti-cancer agents. Enablement, or utility, is determined as of the application filing date. *In re Glass*, 492 F.2d 1228, 1232, 181 USPQ 31, 34 (CCPA 1974). The Kluge declaration, though dated after applicants' filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. *In re Marzocchi*, 439 F.2d at 224 n. 4, 169 USPQ at 370 n. 4. It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility).

[7] The prior art further supports the conclusion that one skilled in the art would be convinced of the applicants' asserted utility. As previously mentioned, prior art--Zee Cheng et al. and Paull--disclosed structurally similar compounds which were proven ***in vivo*** against various tumor models to be effective as chemotherapeutic agents. Although it is true that minor changes in chemical compounds can radically alter their effects on the human body, *Kawai*, 480 F.2d at 891, 178 USPQ at 167, evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility. *See Rey-Bellet v. Engelhardt*, 493 F.2d 1380, 181 USPQ 453 (CCPA 1974); *Kawai*, 480 F.2d 880, 178 USPQ 158.

The Commissioner counters that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means *in vivo* testing in humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans. [FN20] The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. *See Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed.Cir.1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.").

> FN20. We note that this discussion is relevant to the earlier discussion as well. If we were to conclude that these *in vivo* tests are insufficient to establish usefulness for the claimed compounds, that would bear on the issue of whether one skilled in the art would, in light of the structurally similar compounds in Paull and Zee Cheng et al., have cause to doubt applicants' asserted usefulness for the compounds.

Our court's predecessor has determined that proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility. *In re Krimmel*, 292 F.2d 948, 953, 130 USPQ 215, 219 (CCPA 1961); *see also In re Bergel*, 292 F.2d 958, 130 USPQ 205 (CCPA 1961). In concluding that similar *in vivo* tests were adequate proof of utility the court in *In re Krimmel* stated:

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans.

Krimmel, 292 F.2d at 953, 130 USPQ at 219. Moreover, NCI apparently believes these tests are statistically significant because it has explicitly recognized both the P388 and L1210 murine tumor models as standard screening tests for determining whether new ***1568** compounds may be useful as antitumor agents.

In the context of this case the Martin and Pazdur references, on which the Commissioner relies, do not convince us otherwise. Pazdur only questions the reliability of the screening tests against lung cancer; it says nothing regarding other types of tumors. Although the Martin reference does note that some laboratory oncologists are skeptical about the predictive value of ***in vivo*** murine tumor models for human therapy, Martin recognizes that these tumor models continue to contribute to an increasing human cure rate. In fact, the authors conclude that this perception (i.e. lack of predictive reliability) is not tenable in light of present information.

On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical studies. *See* 21 U.S.C. § 355(i)(1); 21 C.F.R. § 312.23(a)(5), (a)(8) (1994). Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions.

The purpose of the Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimes. *See* 21 C.F.R. § 312.21(b).

[8] FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

In view of all the foregoing, we conclude that applicants' disclosure complies with the requirements of 35 U.S.C. § 112 ¶ 1.

3.

[9] The Commissioner takes this opportunity to raise the question of this court's standard of review when deciding cases on appeal from the PTO. Traditionally we have recited our standard of review to be, with regard to questions of law, that review is without deference to the views of the Agency, *In re Donaldson*, 16 F.3d 1189, 1192, 29 USPQ2d 1845, 1848 (Fed.Cir.1994) (in banc), *In re Caveney*, 761 F.2d 671, 674, 226 USPQ 1, 3 (Fed.Cir.1985), and with regard to questions of fact, we defer to the Agency unless its findings are "clearly erroneous." *See, e.g., In re Baxter Travenol Labs*, 952 F.2d 388, 21 USPQ2d 1281 (Fed.Cir.1991); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed.Cir.1990); *In re De Blauwe*, 736 F.2d 699, 222 USPQ 191 (Fed.Cir.1984).

[10] With regard to judgment calls, those questions that fall "[s]omewhere near the middle of the fact-law spectrum," this court has recognized "the falseness of the fact-law dichotomy, since the determination at issue, involving as it does the application of a general legal standard to particular facts, is probably most realistically described as neither of fact nor law, but mixed." *Campbell v. Merit Systems Protection Board*, 27 F.3d 1560, 1565 (Fed.Cir.1994). When these questions of judgment are before us, whether we defer, and the extent to which we defer, turns on the nature of the case and the nature of the judgment. *Id.* ("Characterization therefore must follow from an *a priori* decision as to whether deferring ... is sound judicial policy. We would be less than candid to suggest otherwise.").

The Commissioner contends that the appropriate standard of review for this court regarding questions of law, of fact, and mixed questions of law and fact, coming to us from the PTO is found in the Administrative Procedure Act (APA) at 5 U.S.C. § 706. The standard set out there is that "[t]he reviewing court shall ... hold unlawful and set aside agency action, findings, and conclusions found to be--(A) arbitrary, capricious, an ***1569** abuse of discretion, or otherwise not in accordance with law; ... (E) unsupported by substantial evidence...." The Commissioner is of the view that the stated standard we now use, which is the traditional standard of review for matters coming from a trial court, is not appropriate for decisions coming from an agency with presumed expertise in the subject area, and is not in accord with law. [FN21]

> FN21. Congress enacted the Administrative Procedure Act (APA) on June 11, 1946. *See* 1 Kenneth Culp Davis, Administrative Law Treatise, § 1:7 (2d ed. 1978). The APA sets forth a framework for administrative agency procedure and provides judicial review for persons adversely affected by final agency actions. Chapter 7, codified at 5 U.S.C. § 701-706, contains the APA judicial review provisions, including the standard of review provision quoted above.

Applicants argue that by custom and tradition, recognized by the law of this court, the standard of review we have applied, even though inconsistent with the standard set forth in the APA, nevertheless is a permissible standard. In our consideration of this issue, there is a reality check: would it matter to the outcome in a given case which formulation of the standard a court articulates in arriving at its decision? The answer no doubt must be that, even though in some cases it might not matter, in others it would, otherwise the lengthy debates about the meaning of these formulations and the circumstances in which they apply would be unnecessary.

A preliminary question, then, is whether this is one of those cases in which a difference in the standard of review would make a difference in the outcome.

The ultimate issue is whether the Board correctly applied the § 112 ¶ 1 enablement mandate and its implicit requirement of practical utility, or perhaps more accurately the underlying requirement of § 101, to the facts of this case. As we have explained, the issue breaks down into two subsidiary issues: (1) whether a person of ordinary skill in the art would conclude that the applicants had sufficiently described particular diseases addressed by the invention, and (2) whether the Patent Act supports a requirement that makes human testing a prerequisite to patentability under the circumstances of this case.

The first subsidiary issue, whether the application adequately described particular diseases, calls for a judgment about what the various representations and discussions contained in the patent application's specification would say to a person of ordinary skill in the art. We have considered that question carefully, and, for the reasons we explained above in some detail, we conclude that the Board's judgment on this question was erroneous. Our conclusion rests on our understanding of what a person skilled in the art would gather from the various art cited, and from the statements in the application itself. We consider the Board's error to be sufficiently clear that it is reversible whether viewed as clear error or as resulting in an arbitrary and capricious decision.

The second subsidiary issue, whether human testing is a prerequisite to patentability, is a pure question of law: what does the practical utility requirement mean in a case of this kind. Under either our traditional standard or under the APA standard no deference is owed the Agency on a question of law, and none was accorded.

If the question concerning the standard of review, raised by the Commissioner, is to be addressed meaningfully, it must arise in a case in which the decision will turn on that question, and, recognizing this, the parties fully brief the issue. This is not that case. We conclude that it is not necessary to the disposition of this case to address the question raised by the Commissioner; accordingly, we decline the invitation to do so.

III. CONCLUSION

The Board erred in affirming the examiner's rejection under 35 U.S.C. § 112 ¶ 1. The decision is reversed.

REVERSED.

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C

United States Court of Customs and Patent Appeals.
Application of Walter L. BORKOWSKI and John J. Van Venrooy.
Patent Appeal No. 8214.

March 12, 1970.

The Patent Office Board of Appeals affirmed rejection of certain claims for a process producing oxygenated hydrocarbons by reacting hydrocarbons with ferric chloride in the vapor phase and hydrolyzing the resulting chlorohydrocarbon. The applicants appealed. The Court of Customs and Patent Appeals, Rich, Acting C.J., held that a specification in a patent application is not required to contain a working example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation, and a few hours' experimentation may not be an undue amount considering the nature of the claimed invention, and if the scope of the subject matter embraced by the claim for a patent is clear, and if the applicant has not otherwise indicated that he intends claims to be of a different scope, then the claim does particularly point out and distinctly claim the subject matter which applicant regards as his invention, even if the 'enabling' disclosure of the specification is not commensurate in scope with the subject matter encompassed by the claim.

Reversed as to certain claims and affirmed as to others.

West Headnotes

[1] **Patents** 99
291k99 Most Cited Cases
Specification in patent application is not required to contain working example if invention is otherwise disclosed in such manner that one skilled in art will be able to practice it without undue amount of experimentation, and a few hours' experimentation may not be undue amount considering nature of claimed invention. 35 U.S.C.A. § 112.

[2] **Patents** 101(5)
291k101(5) Most Cited Cases
Statute requiring specification in patent application requires claims which
point out and distinctly claim subject matter sought to be patented, rather than "the invention." 35 U.S.C.A. § 112.

[3] **Patents** 101(9)
291k101(9) Most Cited Cases
If scope of subject matter embraced by claim for patent is clear, and if applicant has not otherwise indicated that he intends claim to be of different scope, then claim does particularly point out and distinctly claim subject matter which applicant regards as his invention, even if "enabling" disclosure of specification is not commensurate in scope with subject matter encompassed by claim. 35 U.S.C.A. § 112.

[4] **Patents** 101(9)
291k101(9) Most Cited Cases
If "enabling" disclosure of specification for patent is not commensurate in scope with subject matter encompassed by claim, claim is based on insufficient disclosure and should be rejected on such ground and not on ground that claim is imprecise or indefinite or otherwise not in compliance with portion of statute requiring specification to conclude with one or more claims pointing out and claiming subject matter which applicant regards as his invention. 35 U.S.C.A. § 112.

[5] **Patents** 101(9)
291k101(9) Most Cited Cases
Disclosure of patent application may be insufficient to support one claim but sufficient to support another. 35 U.S.C.A. § 112.

[6] **Patents** 97
291k97 Most Cited Cases

[6] **Patents** 111
291k111 Most Cited Cases
Examiner and Patent Office Board of Appeals upon rejection should make clear whether claim is regarded as unclear or whether disclosure of specification is regarded as inadequate to support it. 35 U.S.C.A. § § 102, 112.

[7] **Patents** 101(5)
291k101(5) Most Cited Cases

[7] **Patents** 101(6)
291k101(6) Most Cited Cases
Claims for process for producing oxygenated hydrocarbons by reacting them with ferric chloride in vapor phase and hydrolyzing resulting chlorohydrocarbon were not unduly broad or

indefinite because of use of term "hydrocarbon" where claims were limited to hydrocarbons in vapor phase at reaction temperature and thus did not call for just any hydrocarbon. 35 U.S.C.A. § 112.

****905 *947** Barry A. Bisson, Wilmington, Del., attorney of record, for appellants.

Joseph Schimmel, Washington, D.C., for the Commissioner of Patents. Jack E. Armore, Washington, D.C., of counsel.

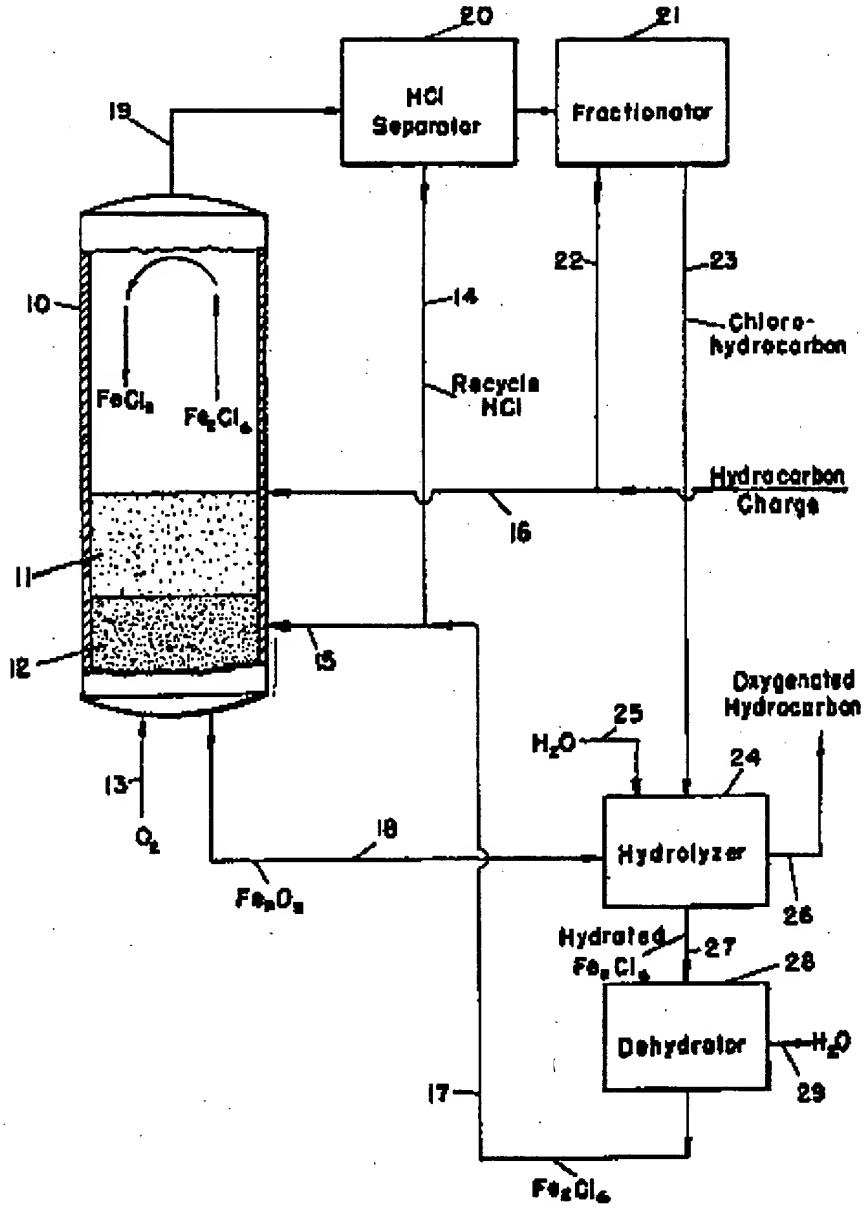
Before RICH, Acting Chief Judge, ALMOND, BALDWIN and LANE, Judges, and MATTHEWS, Senior Judge, United States District Court for the District of Columbia, sitting by designation.

RICH, Acting Chief Judge.

This appeal is from the decision of the Patent Office Board of Appeals affirming the rejection of claims 7-12 of application serial No. 144,221, filed October ****906** 10, 1961, entitled 'Preparation of Oxygenated Hydrocarbons.' No claim is allowed.

The claimed invention is a process for producing oxygenated hydrocarbons such as alcohols, glycols, aldehydes, and acids by reacting hydrocarbons with ferric chloride in vapor phase and hydrolyzing the resulting chlorohydrocarbon. The reaction of ferric chloride with hydrocarbons is commonly referred to in the art as 'ferrichlorination.'

The following drawing from appellants' specification is a schematic illustration of the process:



**907 *949 When read with reference to this drawing, claim 7 sufficiently describes the process for the purposes of this opinion: [FN1]

FN1. It will help, in following the claim, to know that:
ferric chloride is 'Fe(2)Cl(6)' shown in reactor 10 and in lines 15 and 27;
ferric oxide is 'Fe(2)O(3)' shown in the reactor at 12 and in line 18;
solid ferrous chloride is 'FeCl(2)' shown in the reactor at 11;
oxygen is 'O(2)' introduced into the reactor at 13;
hydrogen chloride is 'HCl'; and the end product of the process is the 'Oxygenated Hydrocarbon' at center right of the drawing.

7. Method of preparing oxygenated hydrocarbon which comprises:

(a) feeding hydrocarbon in vapor phase at an intermediate level into a reactor maintained at a temperature in the range of 315-500 degrees C., said hydrocarbon being a vapor at the selected reaction temperature and said reactor containing beneath the level of hydrocarbon introduction a bed of iron compounds comprising a ferrous chloride mass in its upper part and a ferric oxide mass in its lower part,

(b) feeding gaseous ferric chloride into said reactor and reacting it with the hydrocarbon above said bed, whereby chlorination of hydrocarbon occurs with the formation of by-product hydrogen chloride and the ferric chloride is reduced to solid ferrous chloride which falls downwardly to said bed,

(c) removing a mixture of chloro-hydrocarbon and hydrogen chloride from the upper part of said reactor,

(d) recovering hydrogen chloride from the mixture,

(e) introducing the hydrogen chloride into the bed at a level near the top of the ferric oxide mass,

(f) passing oxygen into the ferric oxide mass beneath the level of introduction of the hydrogen chloride,

(g) flowing said oxygen upwardly through the bed and in contact with the ferrous chloride, whereby the ferrous chloride is continuously converted in part to gaseous ferric chloride and in part to ferric oxide,

(h) removing ferric oxide from the bottom of said reactor,

(i) contacting said chlorohydrocarbon with water at a temperature in the range of 100-200 degrees C. and in the presence of the removed ferric oxide, whereby the chlorohydrocarbon is hydrolyzed to oxygenated hydrocarbon and the ferric oxide is converted to hydrated ferric chloride,

(j) dehydrating the ferric chloride,

(k) and recycling the dehydrated ferric chloride to said reactor in amount substantially equivalent to the ferric oxide removed therefrom.

Claim 8 depends from claim 7 and recites a preferred temperature range of 350- 425 degrees C. for step (a); claims 9 and 10 depend, respectively, from claim 8 and 7 and recite a preferred temperature range of 120-160 degrees C. for step (i); and claims 11 and 12 each depend from claim 7 and require, respectively, that the 'hydrocarbon' be 'methane' and 'ethane.'

The examiner rejected claims 7-12 'as based on an insufficient disclosure under 35 U.S.C. 112' and claims 7-10 as failing to 'particularly point out and distinctly claim the invention as required by 35 U.S.C. 112.' There is no art rejection.

***950** [1] With respect to the first rejection, the examiner was of the opinion that appellants' description of their invention 'is not such that it would enable one skilled in the art to practice the present invention, particularly with reference to the chlorination step.' He mentioned 'relative amounts of the 'hydrocarbon" and 'magnitude of reaction times' as two parameters which appellants should have disclosed more fully and, while acknowledging that a specification need not 'read as instructions to a technician' and that 'perhaps one might after a few hours of experimentation, determine how to carry out and ****908** control the chlorination of the simplest hydrocarbon, methane,' the examiner stated:

But the whole purpose of Section 112 is to obviate the necessity for such experimentation. Moreover, the conditions are obviously not the same for methane as they are for the myriad of other hydrocarbons contemplated and urged to be suitable for use in the instant process.

Sustaining this rejection, the board stated, inter alia:

The Examiner has pointed to the possible variations in the time of chlorination, probably because this is a demonstratably variable and important parameter. The disclosure, though, is no more deficient in this respect than with respect to any other of its values which would help to illustrate the 'mode of operation' in which appellants believe their invention to lie. Appellants do not believe that the time of chlorination is a critical aspect of their process and, probably, if you consider this as a single parameter they are correct in this, but the asserted novelty in the mode of operation which invites a careful balance of a number of distinct reactions makes illustration particularly necessary. Desirably and necessarily, such illustration should provide an exemplary correlation of the times of reaction, rates of reactant, feed and material removal (chlorinated product, ferric oxide, HCl, etc.). This would inform a man skilled in the art of the actual feasibility of appellants' process, and provide some sort of jumping off place in a plunge into the unknown when planning a series of experiments from which the necessary operating parameters of the process may be determined.

The 'exemplary correlation' which the board considered necessary would appear to be nothing more nor less than a specific working example. However, as we have stated in a number of opinions, [FN2] a specification need not contain a working example if the invention is otherwise disclosed in

such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. Here, while it may be that an 'exemplary correlation' of parameters such as times of reaction and rates of reactant feed and product removal would give the worker in the art some useful information and provide a 'jumping off place,' we see no basis for concluding that without such information the worker in the art would ***951** not be enabled by the specification to practice the invention, i.e., to 'balance' the several reactions involved in appellants' process. The 'few hours' experimentation mentioned by the examiner certainly would not seem to be an undue amount of time considering the nature of the claimed invention. We therefore cannot agree with the reasons given by the examiner and the board for concluding that appellants' specification does not comply with § 112. The rejection of claims 7-12 'as being based on an insufficient disclosure' is accordingly reversed.

> FN2. E.g., In re Long, 368 F.2d 892, 54 CCPA 835 (1966), and cases cited therein. Compare Minerals Separation, Ltd. v. Hyde, 242 U.S. 261, 270, 271, 37 S.Ct. 82, 61 L.Ed. 286 (1916).

As above stated, the examiner additionally rejected claims 7-10 'for failing to particularly point out and distinctly claim the invention as required by 35 U.S.C. § 112.' This language is that of the second paragraph of 112, first sentence. The examiner was of the opinion that claims 7-10 'are unduly broad and indefinite in the recitation of the 'hydrocarbon' reactant,' his reasons being as follows:

This term ('hydrocarbon') encompasses an almost limitless number of compounds, and, hence, is not adequately supported by the somewhat limited disclosure. The salient absence of a representative example for the various types of hydrocarbons alleged to be suitable for use in the instant ****909** process further render(s) the support for the breadth of the claims on appeal inadequate.

We have two difficulties with these reasons. First, since the rejection of the claims is predicated only on criticisms of the disclosure portion of the specification, we do not see how they are relevant to that portion of the second paragraph of § 112 from which the examiner was quoting, namely, the first sentence, which pertains only to claims and reads in full:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which applicant regards as his invention.

And, second, regardless of the relevance of these criticisms to the requirements of the second paragraph of § 112, we do not find the criticisms to have merit.

[2] With respect to our first difficulty, the examiner's apparent paraphrase of the first sentence of the second paragraph of § 112 is incomplete in a most important respect. While the examiner states the requirement to be claims which 'particularly point out and distinctly claim the invention,' § 112 actually requires claims 'particularly pointing out and distinctly claiming the subject matter which applicant regards as his invention.' In reality, this means that applicant must particularly point out and distinctly claim the subject matter sought to be patented.

***952** [3][4][5][6] The examiner's approach to determining whether appellants' claims satisfy the requirements of § 112 appears to have been to study appellants' disclosure, to formulate a conclusion as to what he (the examiner) regards as the broadest invention supported by the disclosure, and then to determine whether appellants' claims are broader than the examiner's conception of what 'the invention' is. We cannot agree that § 112 permits of such an approach to claims. The first sentence of the second paragraph of § 112 is essentially a requirement for precision and definiteness of claim language. If the scope of subject matter embraced by a claim is clear, and if the applicant has not otherwise indicated that he intends that claim to be of a different scope, [FN3] then the claim does particularly point out and distinctly claim the subject matter which the applicant regards as his invention. That is to say, if the 'enabling' disclosure of a specification is not commensurate in scope with the subject matter encompassed by a claim, that fact does not render the claim imprecise or indefinite or otherwise not in compliance with the second paragraph of § 112; rather, the claim is based on an insufficient disclosure [FN4] (§ 112, first paragraph) and should be rejected on that ground. See In re Fuetterer, 319 F.2d 259, 50 CCPA 1453 (1963); In re Kamal, 398 F.2d 867, 55 CCPA 1409 (1968); and In re Wakefield (PA 8192), Cust. & Pat.App., 422 F.2d 897, decided concurrently herewith. Thus, just as a claim which is of such breadth that it reads on subject matter disclosed in the prior art is rejected under § 102

rather than under the second paragraph of § 112, a claim which is of such breadth that it reads on subject matter as to which the specification is not 'enabling' should be rejected under the first paragraph of § 112 rather than the second. We do not intend hereby to suggest that rejections under § 112 must be labeled 'first paragraph' or 'second paragraph.' What we do suggest is that it should be made clear exactly which of the several requirements of § 112 are thought not to have been met. Is the claim unclear or is the specification's disclosure inadequate to support it?

> FN3. See In re Prater, 415 F.2d 1393, 56 CCPA 1381 (1969), where the applicant did indicate an intended scope different from our interpretation.
>
> FN4. A disclosure may, of course, be insufficient to support one claim but sufficient to support another.

[7] As to the merits of the conclusions and reasons upon which the examiner based this rejection, we do not agree either that claims 7-10 are rendered 'unduly ****910** broad' or 'indefinite' by the term 'hydrocarbon' or that a 'representative example for the various types of hydrocarbons' is needed. As appellants point out, claims 7-10 are limited to hydrocarbons which are in the vapor phase at the reaction temperature and thus do not call for just any hydrocarbon. Moreover, there is no magical relation between the number of representative ***953** examples and the breadth of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling' and sets forth the 'best mode contemplated.'

The board did not expressly accept or reject the examiner's reasons for separately rejecting claims 7-10 under § 112, second paragraph. Instead, the board 'affirmed' this rejection while observing for the first time that although appellants' specification suggests that the hydrocarbon used in their process must be one which, upon being ferrichlorinated, will yield a chlorinated product maintainable in vapor phase at the reaction temperature, claims 7-10 contain no corresponding limitation. [FN5] On this point the board said:

> FN5. In this regard, the specification states: The above-described portion of the process is applicable to the ferrichlorination of any hydrocarbon stock which is a vapor at the selected reaction temperature within the range of 315-500 degrees C. and whose chlorination products can be maintained in vapor phase at such temperature level.

The requirement that the product be a vapor is obviously an important one because we find no description in the specification of how the liquid and solid products and by-products are to be removed from the chlorination vessel.

Although this statement relates only to alleged deficiencies of the specification and although, as pointed out above, such deficiencies give rise to rejections under the first and not the second paragraph of § 112, appellants have not complained that they were misled by this confusion nor do they dispute that claim 7 (and claims 8-10 by dependence) should contain the additional limitation. Neither have appellants sought to have the board denominate the raising of this issue a new ground of rejection under Rule 196(b). Accordingly, we are constrained to affirm the decision of the board as to claims 7-10.

However, we note that in a Request for Reconsideration addressed to the board, appellants asked, inter alia, that

* * * a new decision be made, in accordance with Rule 196(c), which includes an explicit statement that Claims 7-10 may be allowed if they are amended by the applicants to include the limitation that the chlorinated products be maintained in vapor phase at the reaction temperature.

Rule 196(c) provides:

(c) Should the decision of the Board of Appeals include an explicit statement that a claim may be allowed in amended form, applicant shall have the right to amend in conformity with such statement which shall be binding on the primary examiner in the absence of new references or grounds of rejection.

The board refused appellants' request, saying only:

We find no acceptable basis for the requested recommendation as to claims 7 to 10.

***954** Apparently, the board declined to act pursuant to Rule 196(c) because the rejection of all the claims under the first paragraph of § 112, which it affirmed, still would have prevented the claims from being 'allowed in amended form.' Inasmuch as (1) we have reversed this other rejection, (2) the necessity of

amending claims 7-10 to include the additional limitation was first asserted by the board, and (3) appellants have had no opportunity to so amend their claims (as they clearly are willing to do), we suggest that the board consider whether, under these circumstances, a recommendation under Rule 196(c) is now in order.

****911** The decision of the board is reversed as to claims 11 and 12 and affirmed as to claims 7-10.

***947** Modified.

57 C.C.P.A. 946, 422 F.2d 904, 164 U.S.P.Q. 642

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□

Cross et al.
v.
Iizuka et al.

Court of Appeals, Federal Circuit

No. 84-1111

Decided Jan. 28, 1985
United States Patents Quarterly Headnotes

PATENTS
[1] Patentability -- Utility (§ 51.75)
Board did not err in finding that in vitro utility disclosed in foreign priority application is sufficient to establish practical utility under 35 USC 101.

PATENTS
[2] Patentability -- Utility (§ 51.75)
Rigorous correlation of pharmacological activity between disclosed in vitro utility and in vivo activity is not necessary where disclosure of pharmacological activity is reasonable based upon probative evidence.

PATENTS
[3] Patentability -- Utility (§ 51.75)
35 USC 112 "how to use" requirement is satisfied, despite failure of disclosure to reveal dosages for novel compound per se, those skilled in art having had sufficient information at critical date to determine dosage for desired pharmacological activity.

PATENTS
Particular patents -- Imadazole Derivatives
Iizuka, et al., application, Imidazole Derivatives, award of priority over Cross et al., application, N-(Phenoxyalkyl) Imidazoles as Selective Inhibitors of the Thromboxane Synthetase Enzyme and Pharmaceutical Compositions Thereof, affirmed.

***740** Appeal from Patent and Trademark Office Board of Patent interferences.

Patent interference No. 100,650, between Peter E. Cross, et al., application, Serial No. 95,755, filed Nov. 19, 1979, and Kinji Iizuka, et al., application, Serial No. 68,365, filed Aug. 21, 1979. From decision awarding priority to party Iizuka, party Cross, et al. appeals. Affirmed.

Rudolf E. Hutz, and Connoly, Bove, Lodge & Hutz, both of Wilmington, Del. (Thomas M. Meshbesher, Wilmington, Del., on the brief) for appellants.

Peter D. Olexy, and Sugrue, Mion, Zinn, MacPeake & Seas, both of Washington, D.C. (Thomas J. MacPeak, Washington, D.C., on the brief) for appellees.

Before Kashiwa, Bennett, and Bissell, Circuit Judges.

Kashiwa, Circuit Judge.

This appeal is from the decision of the United States Patent and Trademark Office (PTO) Board of Patent Interferences (Board) awarding priority on the single phantom count to Iizuka, et al. (Iizuka), the senior party. We affirm.

Background

Interference No. 100,650 was declared on 20 April 1981 between application serial No. 68,365, for "Imidazole Derivatives," filed by Iizuka on 21 August 1979 and application serial No. 95,755, for "N-(Phenoxyalkyl) Imidazoles as Selective Inhibitors of the Thromboxane Synthetase Enzyme and Pharmaceutical Compositions Thereof," filed by Cross, et al. (Cross) on 19 November 1979. The single phantom count of the interference is directed to imidazole derivative compounds and reads as follows:

> A compound selected from the group consisting of an imidazole derivative of the formula
>
> □wherein R is a hydrogen atom or an alkyl group having 1 to 6 carbon atoms, each of Asub1 or Asub2 , which may be the same or different, are alkylene having 1 to 8 carbon atoms, m is 0 or 1, X is oxygen or sulfur, and each of Rsub1 or Rsub2 , which may be the same or different, is a hydrogen atom *or an alkyl group having 1 to 6 carbon* atoms; Rsub3 is H, Csub1 -Csub4 alkyl, Csub1 -Csub4 alkoxy or halogen; and the pharmaceutically acceptable salts thereof. [FN1]

The applications of Cross and Iizuka both disclose inventions directed to imidazole derivative

compounds which inhibit the synthesis of thromboxane synthetase, an enzyme which leads to the formation of thromboxane Asub2 (TXAsub2) [FN2] a highly unstable, biologically active compound which is converted to stable thromboxane Bsub2 by the addition of water. Thromboxane Asub2 , as of the time period during which the applications were filed, was postulated to be a causal factor in platelet ***741** aggregation. [FN3] Platelet aggregation is associated with several deleterious conditions in mammalia, including humans, such as platelet thrombosis, pulmonary vasoconstriction or vasospasm, inflammation, hypertension, and collagen-induced thrombosis.

Pursuant to 37 C.F.R. § 1.231(a)(4) each party moved to be accorded the benefit of a foreign priority application under 35 U.S.C. § 119, Cross claiming priority based upon a British application filed 13 December 1978, and Iizuka claiming priority based upon a Japanese application filed 21 August 1978. Each party opposed the motion of the other party, each party contending that the other party's foreign priority application did not comply with the disclosure requirements of 35 U.S.C. § 112.

The primary examiner granted each party's motion, noting that the utility alleged in each application was of a pharmacological nature, i.e., the inhibition of thromboxane synthetase, and that inasmuch as the single phantom count of the interference was directed to a compound, it was not necessary that utility be established by tests and dosages with respect to human beings. The examiner found that one of ordinary skill in the art would know how to use the imidazole derivatives, i.e., be able to determine specific dosages, for biological purposes. Based upon the filing dates of the foreign priority applications, [FN4] Iizuka was declared the senior party and a show cause order was issued against Cross.

Cross requested a final hearing on the issue of the sufficiency of the Japanese priority application of Iizuka, and moved for a testimony period to present evidence on this issue. A testimony period was granted over the opposition of Iizuka, and Cross took the testimony of his expert witness, Dr. Smith, and Iizuka took the testimony of his expert witness, Dr. Ramwell and also proferred several exhibits pursuant to 37 C.F.R. § 1.282. All testimony and exhibits related to the sufficiency of Iizuka's Japanese priority application, i.e., whether it complied with the disclosure requirements of 35 U.S.C. § 112.

Decision of the Board

The Board noted that the sole issue before it was whether Iizuka was entitled to the benefit of his Japanese priority application. [FN5] Relying on In re Bundy, 642 F.2d 430, 209 USPQ 48 (CCPA 1981), and Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881 (CCPA 1980), the Board held that tests evidencing pharmacological activity may manifest a practical utility even though they may not establish a specific therapeutic use. The Board found that the Japanese priority application disclosed pharmacological activity in the similar activity of the imidazole derivatives of the count to imidazole and 1-methylimidazole, which possess an inhibitory action for thromboxane synthetase, and that practical utility was disclosed in the strong inhibitory action for thromboxane synthetase from human or bovine platelet microsomes, i.e., an in vitro utility. [FN6]

***742** The Board further found that the Japanese priority application disclosed "how-to-use" knowledge directed to the practical utility in a microsome system, and that microsome assays were admittedly known in the art. A skilled worker could determine the relative strength of the imidazole compounds of the count vis-a-vis the known parent imidazole and 1-methylimidazole compounds for use in the microsome assay milieu. Knowledge of the pharmacological activities of compounds is beneficial to the medical profession, and requiring Iizuka to have disclosed in vivo dosages in the Japanese priority application would delay and frustrate researchers by failing to provide an incentive for early public disclosure of such compounds, thereby failing to further the public interest.

Accordingly, the Board held that the Japanese priority application contained an adequate how-to-use disclosure for the practical utility stated therein.

Issues

Whether the Board erred in finding that the utility disclosed in the Japanese priority application is sufficient to meet the practical utility requirement of 35 U.S.C. § 101.

Whether the Board erred in finding that the Japanese priority application contained sufficient disclosure to satisfy the enablement, i.e., how-to-use, requirement of 35 U.S.C. § 112. [FN7]

Opinion

Proper resolution of the issues before this court necessitates that we address, seriatim, the following questions: (1) What utility is disclosed by the Japanese priority application? (2) Does this stated

utility comply with the "practical utility" requirement of 35 U.S.C. § 101, as delimited by prior decisions of the judiciary? [FN8] (3) Does the Japanese priority application contain sufficient disclosure to meet the how-to-use requirement of § 112 with respect to the stated utility?

It is axiomatic that an invention cannot be considered "useful," in the sense that a patent can be granted on it, unless substantial or practical utility for the invention has been discovered and disclosed where such utility would not be obvious. Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). Where a constructive reduction to practice is involved, as contrasted to an actual reduction to practice, a practical utility for the invention is determined by reference to, and a factual analysis of, the disclosures of the application. Kawai v. Metlesics, 480 F.2d 880, 178 USPQ 158 (CCPA 1973).

1. Japanese Priority Application

The Board factually analyzed the Japanese priority application and found that the only effective disclosure relating to a stated utility for the imidazole derivative compounds of the phantom count was the following:

> [The compounds disclosed] are useful for treatment of inflammation, thrombus, hypertension, cerebral apoplexy, asthma, etc.
>
> Up to this time, it is a known fact that imidazole and 1-methylimidazole posses an inhibitory action for thromboxane synthetase and inhibit a biosynthesis of thromboxane Asub2 . (Prostaglandins, Vol. 13, pages 611- 1977). However, since their inhibitory effect is not satisfactory one, these compounds have not been put to practical use yet as therapeutical medicines for diseases caused by thromboxane Asub2 , such as inflammation, hypertension, thrombus, cerebral apoplexy, asthma, etc.
>
> To develop some compounds possessing a strong inhibitory action for biosynthesis of thromboxane Asub2 , the present inventors devoted themselves to study for various imidazole derivatives, and as a result, found that the compounds [of this invention] possess a strong inhibitory action for ***743** thromboxane synthetase from human or bovine platelet microsomes and are extremely useful as therapeutically active agents for diseases caused by thromboxane Asub2 , for example, inflammation, hypertension, thrombus, cerebal apoplexy, asthma, etc., and thus were proposed this invention based upon those findings.
>
> The imidazole derivatives * * * of this invention are novel compounds which are not described in literature, and which possess a strong inhibitory action for thromboxane synthetase from human or bovine platelet microsomes, and which exhibit a strong inhibitory action for biosynthesis of thromboxane Asub2 in mammalia including human. In general, a satisfactory inhibitory effect is found at a level of molar concentrations of 2.5 x 10 super-8 , for example, 2-[p-(1-imidazolylmethyl)phenoxy]-acetic acid hydrochloride produce the about 50% inhibitory effect at the molar concentrations of 2.5 x 10 super-8 . Accordingly, the imidazole derivatives of this invention are extremely useful as therapeutical medicines for diseases caused by thromboxane Asub2 , such as inflammation, hypertension, thrombus, cerebral apoplexy, asthma, etc.

The Board found that these pertinent sections of the Japanese priority application disclosed some activity or utility, namely that the imidazole derivative compounds of the count possess a strong inhibitory action for thromboxane synthetase in human or bovine platelet microsomes. Cross' position is that the stated purpose or *sole* comtemplated utility of the invention of Iizuka is to provide a novel class of compounds which provide "practical use" as "therapeutical medicines for diseases caused by thromboxane Asub2 ," and therefore the Board erred in its finding as to the stated utility of the Japanese priority application.

While recognizing that Kawai constrains an applicant to entitlement to the benefit of only what is disclosed in the foreign priority application and no more, we also recognize that foreign priority applications, as subsequently filed in the PTO, typically have a style and format dissimilar to the arrangement of application elements suggested by 37 C.F.R. § 1.77. In part this arises because of differences in filing requirements in foreign patent offices, and in part because of the awkwardness resulting from direct literal translations from a foreign language to English. Thus, while the factual determination of the stated utility in an application prepared in the United States may be relatively straightforward, [FN9] the factual analysis of a foreign priority application to determine the utility disclosed therein may be more laborious and open to

varying interpretations.

The weakness of Cross' position is that a fair reading of the pertinent sections of the Japanese priority application as set forth above, discloses utility for the imidazole derivative compounds of the phantom count both as an inhibiting agent for thromboxan synthetase in human or bovine platelet microsomes, as found by the Board, and as therapeutically active agents preventing the biosynthesis of thromboxane Asub2 , thereby functioning as a medicine preventing deleterious conditions caused by thromboxane Asub2 , as contended by Cross.

Evidence of any utility is sufficient when the count does not recite any particular utility. Nelson v. Bowler, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980). See also Rey-Bellet v. Englehardt, 493 F.2d 1380, 181 USPQ 453 (CCPA 1974); Knapp v. Anderson, 477 F.2d 588, 177 USPQ 688 (CCPA 1973); Blicke v. Treves, 241 F.2d 718, 112 USPQ 472 (CCPA 1957). Here the Board, which is charged with the factual determination of utility, [FN10] has found that the specification of the Japanese priority application disclosed a utility for the imidazole derivative compounds of the phanton count in the inhibition of thromboxane synthetase in human or bovine platelet microsomes. Inasmuch as the Board is charged with making this factual determination when the issue is raised, inasmuch as they have so done in the instant case, and inasmuch as there is credible evidence to support this factual determination, we are not prepared to say that the Board erred in its ***744** finding as to the stated utility disclosed in the Japanese priority application.

2. Practical Utility

As noted in the preceding part of this opinion, Cross has contended that the Board erred in its finding as to the utility disclosed in the Japanese priority application. This argument may be viewed in a different perspective, we believe, which is that the stated utility in the Japanese priority application, as found by the Board -- the inhibition of thromboxane synthetase in human or bovine platelet microsomes [FN11] -- is not sufficiently correlated to a pharmacological activity [FN12] to be a practical utility. In other words, Cross may be arguing that the minimum acceptable level of utility disclosed in an application claiming a compound having pharmacological activity must be directed to an in vivo utility in order to comply with the practical utility requirement of § 101.

The starting point for a practical utility analysis is Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). The Court in Brenner noted that "a simple, everyday word ["useful," as found in 35 U.S.C. § 101] can be pregnant with ambiguity when applied to the facts of life." Id. at 529, 148 USPQ at 693. While noting that "one of the purposes of the patent system is to encourage dissemination of information concerning discoveries and inventions," id. at 533, 148 USPQ at 695, the Court found that a more compelling consideration in the determination of whether a patent should be granted "is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point -- where specific benefit exists in currently available form -- there is insufficient justification for permitting an applicant to engross what may prove to be a broad field." Id. at 534-35, 148 USPQ at 695. While we recognize that this case concerned a compound derived from a chemical process, we believe Brenner provides broad guidelines which are helpful in ascertaining what constitutes practical utility for compounds having a pharmacological effect.

In Nelson v. Bowley, 626 F.2d 853, 206 USPQ 881 (1980), our predecessor court, the Court of Customs and Patent Appeals, stated that "[k]nowledge of the pharmacological activity of any compound is obviously beneficial to the public" and concluded that "adequate proof of any such utility constitutes a showing of practical utility." Id. at 856, 206 USPQ at 883. [FN13] The tests [FN14] found by the court to be adequate proof of pharmacological activity or practical utility were a rat blood pressure (BP) test and a gerbil colon smooth muscle stimulation (GC-SMS) test. The BP test was an in vivo test, which was deemed by the court to be direct evidence as to the claimed activity, while the GC-SMS test was an in vitro test. [FN15]

The CCPA in Rey-Bellet v. Englehardt, 493 F.2d 1380, 1383, 181 USPQ 453, 454 (1974), stated that where a count contains no limitation related to utility, evidence establishing a substantial utility for any purpose is sufficient to show a reduction to practice. The court held that three in vivo tests [FN16] conducted in the United States prior to the filing of Englehardt's U.S. application failed to establish an actual reduction to practice. The court proceeded, however, to find sufficient evidence in the record to establish that Englehardt had conceived a utility for his compound prior to the filing date of his U.S. application. The evidence the court found to be sufficient was testimony by the inventor that he

believed his compound would exhibit a particular pharmacological activity because of its structural similarity to anther compound which was known to possess the particular pharmacological activity. The court ***745** found that the testimonial evidence of Englehardt was corroborated by two exhibits entered into evidence. The evidence adduced by Englehardt was found by the court to be sufficient proof that Englehardt had conceived that his compound had utility for the particular pharmacological activity prior to his U.S. filing date. The court further noted that this was a completed conception of utility because it appeared that nothing beyond the exercise of routine skill would have been required to demonstrate that Englehardt's compound possessed the particular pharmacological utility. While noting that the actual testing done was not sufficient to establish an actual reduction to practice, the court found that the extensive testing done in vivo on animals was routine in nature and was not, therefore, to be construed as an indicator that extensive research, i.e., inventive skill and/or undue experimentation, was required to resolve perplexing intricate difficulties related to the utilization of the compound for the particular pharmacological activity.

The CCPA in Kawai v. Metlesics, 480 F.2d 880, 178 USPQ 158 (1973), concurred with the finding of the Board that the applicants had failed to prove that their foreign priority application was adequate under the patent laws of the United States. The only disclosure in the foreign priority application relating to the compound of the count was that it exhibited "pharmacological effects on the central nervous system," which the applicants conceded was an inadequate disclosure. The applicants, however, relied upon a patent made of record as indicative of the general knowledge of one skilled in the art, which the applicants contended described a compound closely related to their claimed compound, to show utility or pharmacological activity for the compound of the count as an anticonvulsant. The court agreed with the board that there were sufficient structural dissimilarities between the compounds of the patent and those of the count to preclude reliance on the patent to supplement the disclosure deficiencies of the foreign priority application.

In Knapp v. Anderson, 477 F.2d 588, 177 USPQ 688 (CCPA 1973), the court, citing to Blicke v. Treves, 241 F.2d 718, 112 USPQ 472 (CCPA 1957), stated that "[i]t is well settled that if the counts do not specify any particular use, evidence proving substantial utility for any purpose is sufficient to establish an actual reduction to practice." Id. at 590, 177 USPQ at 690 (emphasis added). Noting that the only utility contemplated for the compounds of the count was as ashless dispersants in lubricant compositions used in internal combustion engines, the court found no error in the Board's holding that there was no actual reduction to practice because only a potential utility had been established, this holding based upon the Board's finding of a lack of correlation between bench tests and actual service conditions in a combustion engine.

The CCPA has held that nebulous expressions, such as "biological activity" or "biological properties," disclosed in a specification convey little explicit indication regarding the utility of a compound. In re Kirk 376 F.2d 936, 941, 153 USPQ 48, 52 (CCPA 1967). But, while agreeing with the Board that the specification failed to disclose a specific allegation of utility for any compound within the scope of the claims, and that reference in the specification to biological properties of the claimed compound was so general and vague as to be meaningless, the court implied that a disclosure in the specification that the requisite properties of the claimed compounds are similar to those of a natural or synthetic hormone of known activity may, in appropriate circumstances, supplement an application to rectify an inadequate disclosure relating to the practical utility for the compound. Id. at 942, 153 USPQ at 53.

Every utility question arising in an interference, in the final analysis, must be decided on the basis of its own unique factual circumstances. Relevant evidence must be judged as a whole for its persuasiveness in determining whether the suggested use for the compound of the count is a practical utility. Cf. Nelson, 626 F.2d at 858, 206 USPQ at 885.

The Board has found that the Japanese priority application of Iizuka disclosed a practical utility for the compounds of the phantom count in the inhibition of thromboxane synthetase in human or bovine platelet microsomes, i.e., an in vitro utility. Clearly, this stated utility as found by the Board has been delimited with sufficient specificity to satisfy the threshold requirements of Kawai and Kirk. The stated utility of the Japanese priority application is directed to a specific pharmacological activity possessed by the imidazole derivatives of the phantom count -- the inhibition of thromboxane synthetase in vitro. Thus, this court on review is not presented with a general allegation of "biological activity" or "biological properties" as was the CCPA in Kirk, nor is reliance on prior art required to ascertain what specific

pharmacological activity the compound of the count possesses, the factual situation confronting the court in Kawai.

The Japanese priority application, moreover, disclosed that it was generally known in the art, as of the critical date, that the parent imidazole and 1-methylimidazole compounds possessed an inhibitory action for thromboxane ***746** synthetase. Reliance on this disclosure in the specification of the pharmacological property of the parent imidazole and 1- methylimidazole compounds, as going towards proof of the pharmacological activity of the imidazole derivatives of the phantom count, is particularly relevant in the instant case, we believe, because Iizuka is not relying on this inference to supplement an inadequate disclosure in the Japanese priority application regarding the pharmacological activity of the compound of the phantom count, but rather is relying on this inference as cumulative probative evidence showing an adequately disclosed practical utility in the Japanese priority application.

This court, in Rey-Bellet and Kawai, has implied that a particular pharmacological activity identified with prior art compounds may have probative value as to the fact that the compound of the count possesses this particular pharmacological activity where there is a structural similarity between the prior art compounds and the compound of the count. Rey-Bellet, 493 F.2d at 1385-87, 181 USPQ at 456-58; Kawai, 480 F.2d at 890-91, 178 USPQ at 166-67. Cross has failed to proffer sufficient evidence or present any persuasive arguments going to the question of significant structural dissimilarities between the parent imidazole and 1-methylimidazole compounds and the imidazole derivatives of the phantom count. [FN17]

The expert of Iizuka, Dr. Ramwell, testified that, as of the critical date, there was an awareness on the part of those skilled in the art that the parent imidazole compound exhibited an inhibitory activity for thromboxane synthetase, in both in vitro and in vivo environments. Dr. Ramwell further testified that there was an awareness by those skilled in the art of a correlation between thromboxane Asub2 and platelet aggregation, namely that thromboxane Asub2 was a mediator in platelet aggregation. Several exhibits proferred by Iizuka corroborated Dr. Ramwell's testimony as to the general knowledge in the art with respect to the inhibitory effect of the parent imidazole compound for thromboxane synthetase. [FN18] Accordingly, the similar pharmacological activity of the parent imidazole and 1-methylimidazole compounds have probative value in the factual determination of practical utility for the compounds of the phantom count inasmuch as Cross has not met the burden of proof to establish structural dissimilarities between the parent imidazole and 1-methylimidazole compounds and the imidazole derivatives of the phantom count. Rey-Bellet, 493 F.2d at 1386-87, 181 USPQ at 457.

The Board found that there was adequate proof that the Japanese priority application disclosed a pharmacological activity for the compounds of the phantom count in inhibiting the action of thromboxane synthetase, similar to the pharmacological activity of the parent imidazole and 1-methylimidazole compounds which were found to possess an inhibitory action for thromboxane synthetase, this disclosed knowledge of the inhibitory ***747** action of the prior art compounds having been corroborated by testimony and documentary evidence. During the proceedings before the Board, the burden of proof rested upon Cross to show that the Japanese priority application was deficient. 37 C.F.R. § 1.257(a). On review, Cross bears the burden of proof to show that the Board erred in finding that the Japanese priority application had adequately disclosed a practical utility. Reviewing the relevant evidence presented to the Board as a whole, we are not persuaded that Cross has met this burden of proof.

> [1] The final question we must address is whether the inhibitory activity for thromboxane synthetase in human or bovine platelet microsomes, i.e., an in vitro utility, is sufficient to comply with the practical utility requirement of § 101. Based upon the facts of this case, we are not persuaded that the Board erred in finding that the in vitro utility disclosed in the Japanese priority application for the compounds of the count is sufficient to establish a practical utility.

Our predecessor court has noted that adequate proof of any pharmacological activity constitutes a showing of practical utility. See, e.g., Nelson, 626 F.2d at 856, 206 USPQ at 883; Rey-Bellet, 493 F.2d at 1383, 181 USPQ at 454. Dr. Ramwell testified that initial testing of compounds for a particular pharmacological activity is typically done in vitro. In vitro testing permits an investigator to establish the rank order of compounds with respect to the particular pharmacological activity, i.e., to determine the relative potency of the compounds. Compounds having the highest ranking or potency are then selected for further testing in vivo. Presumably this is

the accepted practice in the pharmaceutical industry inasmuch as Cross has not proferred any evidence refuting this testimony of Dr. Ramwell, and we note that this practice has an inherent logical persuasiveness. In vitro testing, in general, is relatively less complex, less time consuming, and less expensive than in vivo testing. Moreover, in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. Iizuka has not urged, and rightly so, that there is an invariable exact correlation between in vitro test results and in vivo test results. Rather, Iizuka's position is that successful in vitro testing for a particular pharmacological activity establishes a significant probability that in vivo testing for this particular pharmacological activity will be successful.

As discussed above, Dr. Ramwell testified that the parent imidazole and 1- methylimidazole compounds had been subjected to both in vitro and in vivo testing as of the critical date, this corroborated by documentary evidence, and found to possess an inhibitory effect for thromboxane synthetase. Based upon this, Dr. Ramwell further testified that he would expect that in vivo testing of the imidazole derivatives of the phantom count would show that these compounds also possessed an inhibitory action for thromboxane synthetase, i.e., there would be a reasonable correlation between in vitro test results and in vivo test results. This evidence was found sufficient by the Board as proof that the Japanese priority application had disclosed a completed practical utility for the imidazole derivatives of the phantom count in inhibiting thromboxane synthetase in human or bovine platelet microsomes. Cf. Rey-Bellet, 493 F.2d at 1386-87, 181 USPQ at 457.

[2] Cross argues that the in vitro utility disclosed by the Japanese priority application is not per se useful, and that more sophisticated in vitro tests, using intact cells, or in vivo tests are necessary to establish a practical utility. [FN19] Cross is arguing that there must be a rigorous correlation of pharmacological activity between the disclosed in vitro utility and an in vivo utility to establish a practical utility. We, however, find ourselves in agrement with the Board that, based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. Cf. Nelson, 626 F.2d at 856, 206 USPQ at 883- 83.

Our predecessor court has accepted evidence of in vivo utility as sufficient to establish a practical utility. See, e.g., Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881 (CCPA 1980); In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); Rey-Bellet v. Englehardt, 493 F.2d 1380, 181 USPQ 453 (CCPA 1974).

Opinions of our predecessor court have recognized the fact that pharmacological testing of animals is a screening procedure for testing new drugs for practical utility. See, e.g., In re Jolles, 628 F.2d 1322, 1327, 206 USPQ 885, 890 (CCPA 1980). This in vivo ***748** testing is but an intermediate link in a screening chain which may eventually led to the use of the drug as a therapeutic agent in humans. We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, in vitro testing, may establish a practical utility for the compound in question. Successful in vitro testing will marshal resources and direct the expenditure of effort to further in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vivo utility. Cf. Nelson, 626 F.2d at 856, 206 USPQ at 883.

Today, under the circumstances of the instant case, where the Japanese priority application discloses an in vitro utility, i.e., the inhibition of thromboxane synthetase in human or bovine platelet microsomes, and where the disclosed in vitro utility is supplemented by the similar in vitro and in vivo pharmacological activity of structurally similar compounds, i.e., the parent imidazole and 1-methylimidazole compounds, we agree with the Board that this in vitro utility is sufficient to comply with the practical utility requirement of § 101.

3. Enablement

The Board found that the knowledge as to the use of the pharmacological activity disclosed in the Japanese priority application lay in the fact that the system was a microsome system, microsome systems admittedly being known to those skilled in the art. Employing a microsome assay, the skilled worker could determine the relative strength of the compounds of the count vis-a-vis the known parent imidazole and 1-methylimidazole compounds. Thus, the dosage in the microsome assay milieu could be determined without inventive skill or undue

experimentation.

Since we have agreed with the Board that the practical utility for the imidazole derivatives of the phantom count lies in their pharmacological activity in the microsome environment, the how-to-use requirement of § 112 must be analyzed with reference to the microsome environment. We are confronted with a disclosure, similar to the situation before the court in Bundy, that fails to reveal dosages for the novel compounds per se. 642 F.2d at 434, 209 USPQ at 51. Although the Japanese priority application does disclose the fact that the imidazole derivatives of the phantom count possess a pharmacological activity similar to the parent imidazole and 1-methylimidazole compounds, the priority application, unlike the application in Bundy, does not disclose dosages for the parent imidazole and 1-methylimidazole compounds.

We agree with the Board, however, that this deficiency in the Japanese priority application is not fatal. The testimonial evidence of Dr. Ramwell, corroborated by certain documentary evidence, showed that those skilled in the art had available, at the critical date, information as to approximate dosage levels for the parent imidazole and 1-methylimidazole compounds to produce an IsubC50 effect, i.e., a 50% inhibition of thromboxane synthetase, in a microsome milieu. The objective of the pharmaceutical research undertaken by the parties was to discover imidazole derivatives having a potent inhibitory effect for thromboxane synthetase. Therefore, we believe it is logical, as did the Board, that the starting point for determining IsubC50 dosage levels for the imidazole derivatives of the phantom count would be the IsubC50 dosage levels of the parent imidazole and 1-methylimidazole compounds. The Board found that there was sufficient credible evidence that one skilled in the art, without the exercise of inventive skill or undue experimentation, could determine the IsubC50 dosage level for the imidazole derivatives of the phantom count in the microsome environment. Cf. Bundy, id., 209 USPQ at 51. We do not believe the Board erred in arriving at this conclusion. This is not a case such as In re Gardner, 427 F.2d 786, 166 USPQ 138 (1970), where the CCPA held that the applicant's disclosure was nonenabling because inventive skill and undue experimentation would be required to discover approprite dosages for humans, i.e., a therapeutic use. In the instant case, we are confronted with a pharmacological activity or practical utility, not a therapeutic use.

While we agree with the Board that the disclosure in the Japanese priority application is somewhat confusing with respect to the 2.5 x 10- super8 level of molar concentrations, and that the 2-[p-(1-imidazolylmethyl) phenoxy]-acetic acid hydrochloride compound is outside the phantom count of the interference, this disclosed molar concentration, we believe, does provide some probative value going towards the sufficiency of the Japanese priority application for an enabling disclosure. The disclosed molar concentration would provide sufficient information as to an initial dosage level so that one skilled in the art could determine, without inventive skill or undue experimentation, the necessary molar concentrations for the imidazole derivatives of the phantom cOunt to achieve the desired pharmacological effect, i.e., the 50% inhibition of thromboxane synthetase in human or bovine platelet microsomes.

***749** [3] The Board held the disclosure of the Japanese priority application adequate to satisfy the first paragraph of § 112. The burden is on Cross to show Board error in arriving at this conclusion, and we are not persuaded that Cross has successfully carried this burden. Accordingly, we are satisfied that the how-to-use requirement of § 112 has been complied with by the disclosures of the Japanese priority application.

Affirmed.

FN1 We note a discrepancy, shown underlined in the above count, between the phantom count as set forth by the primary examiner and that reported by the Board in its decision. The phantom count set forth herein is the one propounded by the primary examiner. However, as will become apparent from the ensuing discussion, the substance of the phantom count is not crucial to resolution of the issues presented by this case.

FN2 The formation of TXAsub2 in an arachidonic acid challenge is a sequential process initiated by the conversion of arachidonic acid to postaglandin PGGsub2 by the action of cyclooxygenase, which adds oxygen to the acid. Peroxidase converts the prostaglandin PGGsub2 to prostaglandin PGHsub2 , which in turn is converted by thromboxane synthetase to TXAsub2 .

FN3 Iizuka's position is that, as of the

"critical date" of his application, TXAsub2 was widely accepted in the art as causing platelet aggregation. Cross' position is that, as of the "critical date," platelet aggregation was believed to be nonspecific, i.e., platelet aggregation *may* occur in the presence of thromboxane synthetase, but thromboxane synthetase is not necessary for platelet aggregation. We note in retrospect that THE MERCK INDEX 1345-46 (10th ed. 1983) describes TXAsub2 as inducing irreversible platelet aggregation. More to the point, however, this court has noted that it is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests, nor is the inventor's theory or belief as to how his invention works a necessary element in the specification to satisfy the enablement requirement of 35 U.S.C. § 112. Fromson v. Advance Offset Plate, Inc., 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983).

FN4 Each party relies on the filing date of its foreign priority application to establish a constructive reduction to practice, the earliest date of invention to which each party is entitled under the patent laws of the United States. Kawai v. Metlesics, 480 F.2d 880, 885-86, 178 USPQ 158, 162 (CCPA 1973).

FN5 More specifically, the issue before the Board was whether the Japanese priority application complied with the how-to-use requirement of 35 U.S.C. § 112. Section 112 of Title 35 provides, in pertinent part, that:

The specification shall contain a written description of the invention, of the manner and process of making and *using* it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and *use* the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention. (Emphasis added.)Should Iizuka's Japanese priority application be found nonenabling with respect to the how-to-use requirement of § 112, or otherwise found deficient under the patent laws of the United States, priority would be awarded to Cross based upon his unchallenged entitlement to the benefit of his British application.

FN6 Generally, in vitro refers to an environment outside of a living organism, usually an artificial environment such as a test tube or culture. In contradistinction, in vivo generally refers to an environment within a living organism, such as a plant or animal, or it may refer to a particular portion of an organ external to the living organism, e.g., rat aortic loop.

FN7 Utility is a fact question. Raytheon Co. v. Roper Corp., 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 127 (1984). Enablement under § 112, paragraph 1, i.e., the how-to-use requirement, is a question of law. Id. at 960 n.6, 220 USPQ at 599 n.6.

FN8 While questions one and two are closely connected, a thorough analysis of the utility issue requires first, a determination as to what utility is disclosed, i.e., the stated utility, for the invention claimed in the application. Only after the stated utility has been determined, can a proper analysis be undertaken to determine if the stated utility complies with the "practical utility" requirement of § 101. As noted above, these questions regarding utility are factual in nature, see supra note 7, and are to be determined in the first instance by the PTO, the agency with the expertise in this regard.

FN9 In applications prepared in the United States by experienced patent drafters, the drafter of the application typically sets forth objectives for the invention in the "Summary of the Invention" section of the application. These objectives will normally be consonant with the utility disclosed for the invention. As this court has noted, "[w]hen a properly claimed invention meets at least one stated objective, utility under § 101 is clearly shown." Raytheon Co. v. Roper Corp., 724 F.2d 951, 958, 220 USPQ 592, 598 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 127 (1984).

FN10 Under the facts of the instant case, utility and enablement questions are ancillary to priority. In the interference proceeding, Cross raised the issue as to whether the Japanese priority application contained sufficient disclosure to satisfy § 112. As noted above, see supra note 5, if

Cross prevails on this issue the Japanese priority application would be removed as the basis for awarding priority to Iizuka. See generally 37 C.F.R. § § 1.225, .231, .258.

FN11 A platelet microsome is an in vitro milieu consisting of blood platelets, the small, colorless corpuscles in the blood of all mammals, and other finely granular elements of protoplasm, such as ribosomes, fragmented endoplasmic reticula and mitochondrial christae.

FN12 Generally, pharmacological activity refers to the properties and reactions of drugs, especially with relation to their therapeutic value.

FN13 For purposes of the present opinion, we consider the phrase "substantial utility," as enunciated in Brenner, to be synonymous with the phrase "practical utility" as used in subsequent opinions of the CCPA.

FN14 We recognize that Nelson dealt with tests which were found adequate to establish an actual reduction to practice, as opposed to a constructive reduction to practice. We agree with the Board that principles applicable to a determination of an actual reduction to practice are generally germane to a constructive reduction to practice.

FN15 Both parties admitted that the GC-SMS test adequately simulated in vivo smooth muscle stimulation.

FN16 The three tests, all in vivo type tests carried out on laboratory animals, were: (1) the Mental Health General Screening Test which indicated the physical response, or absence of a response, of test animals to a drug, indicating the presence, or absence, of a desired pharmacological activity; (2) the Tetrabenazine Antagonism Test which screened drugs for antidepressant activity; and (3) the Sidman Avoidance Test which screened drugs for tranquilizing activity.

FN17 Contrary to Cross' contention in the Reply Brief, the evidence of record relied upon by Cross to show significant structural dissimilarity appears to us to be directed to the fact that there is a wide disparity in potency for thromboxane synthetase inhibition between the parent imidazole compound and prior art imidazole derivatives. Cross has not directed our attention to any specific evidence of record which establishes, or tends to establish, significant structural dissimilarities between the basic imidazole compound and the imidazole derivatives of the phantom count. Variation in potency, moreover, is a matter of degree of activity, see Bundy, 642 F.2d at 433, 209 USPQ at 51, but is still indicative of activity. There is no requirement that the compounds have the same degree of activity. Id., 209 USPQ at 51. Moreover, this argument may be construed as a tacit admission that the parent imidazole compound does possess the particular pharmacological activity of inhibiting thromboxane synthetase.Along this line, we note that Dr. Smith, Cross' expert witness, testified generally, based upon the exhibits proffered by Iizuka, see infra note 18, that the parent imidazole compound possessed pharmacological activity for inhibiting thromboxane synthetase, although stating that there was a wide potency spectrum for prior art imidazole derivatives with respect to the parent imidazole compound.Cross has directed the court's attention to the fact that the Japanese priority application, while disclosing that the parent imidazole and 1-methylimidazole compounds possess an inhibitory action for thromboxane synthetase, further discloses that this inhibitory effect is not satisfactory and that the parent imidazole and 1-methylimidazole compounds have not been put to practical therapeutic use. But a therapeutical utility is not necessarily synonymous to a pharmacological activity. Cf. Nelson, 626 F.2d at 856, 206 USPQ at 883.

FN18 For example, Table I in the article "Imidazole: A Selective Inhibitor of Thromboxane Synthetase," PROSTAGLANDINS, Vol. 13, No. 4, April 1977 (Iizuka Exhibit No. 6), lists 1-methylimidazole and the parent imidazole compounds as possessing inhibitory activity for thromboxane synthetase, thereby offering corroboration of Dr. Ramwell's testimony.The Board noted that Iizuka Exhibits 2-6 and 10-12, while inadmissible for the purpose of establishing the truth of what they say on their face, are admissible

> to bolster and support the testimony of Dr. Ramwell, as well as for the purpose of establishing what literature was available to the art at the critical time. Thus, for review purposes, we have examined these exhibits for their corroborating value with respect to Dr. Ramwell's testimony.
>
> FN19 Cross is seemingly arguing that the in vitro disclosure of the Japanese priority application is only a potential utility. See Knapp v. Anderson, 477 F.2d 588, 591, 177 USPQ 688, 691 (CCPA 1973).

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Comparative in vitro effects of AZT and extracts of *Ocimum gratissimum*, *Ficus polita*, *Clausena anisata*, *Alchornea cordifolia*, and *Elaeophorbia drupifera* against HIV-1 and HIV-2 infections

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Abstract

The effects of *Ocimum gratissimum* (GHX-2), *Ficus polita* (GHX-6), *Clausena anisata* (GHX-7), *Alchornea cordifolia* (GHX-26), *Elaeophorbia drupifera* (GHX-27), and AZT on in vitro HIV-1 and HIV-2 replication and cytopathicity were compared. All plant extracts inhibited HIV-1 strain $HTLVIII_B$ cytopathicity, the leaves of GHX-2 and the seeds of GHX-26 having high antiviral indices (110 and 90, respectively). Against HIV-2 strain GH1, the EC_{50} values ranged from <0.005 to 0.075 mg/ml when treatment was started at 40 min after virus adsorption, except for GHX-7 which showed only moderate activity and GHX-26 which had no activity. When treatment was delayed for 2 h, the plant extracts, unlike AZT, were still very effective against HIV-2. Likewise, only the plant extracts were able to attain EC_{90} values when high multiplicity of infection (MOI) with HIV-1 strain GH3 was used when treatment was delayed for 2 h. In Molt-4 cocultures with Molt-4/HIV, early cytopathic effect (CPE) of cell fusion was unaffected by AZT but was completely inhibited by all plants at noncytotoxic concentrations. In addition, GHX-27 was selectively toxic to Molt-4/HIV cells. The plant extracts also inhibited HIV-1 reverse transcriptase (RT) activity at EC_{50} values of <0.01–0.03 mg/ml. HIV-1 proviral DNA copying as determined in a polymerase chain reaction, was completely inhibited by GHX-2 and GHX-6 at 0.011 and 0.015 mg/ml, respectively. GHX-26 and GHX-27 showed only very moderate activity.

Keywords: Medicinal plants; AZT; HIV-1; HIV-2 infections

1. Introduction

Latent HIV infection in helper T lymphocytes, macrophages, and monocytes, abound throughout the lymphoid system at all stages of infection (Embretson et al., 1993). In addition, there is active and progressive HIV infection in lymphoid tissues from early to late stages of the infection (Pantaleo et al,, 1993). Active and progressive HIV infections may be acute or chronic in nature. Chronically infected cells live far longer than acutely infected cells and serve as factories for virus production to attack uninfected cells. Latently infected cells are reservoirs that can be recruited to be active and progressive (Coffin, 1995). So far, no approach has been developed to tackle latently infected cells. Several nucleoside analogs including 3-azido-2′,3′-dideoxythymidine (AZT) have been developed to inhibit virus production and cytopathicity in acutely infected cells (Tuazon and Labriola, 1987; Fischl et al., 1987; Yarchoan et al., 1988). The nucleoside analogs act by inhibiting HIV-specified reverse transcriptase (RT; Tuazon and Labriola, 1987; Coffin, 1990). Rapid mutations engendering drug resistance do occur in *HIV RT* gene in the presence or absence of nucleoside analogs (Mohri et al., 1993). Protease inhibitors have also been shown to inhibit HIV production from chronically infected cells (Erickson et al., 1990; Kempf et al., 1990, 1991; Kort et al., 1993). Unfortunately, poor water solubility of the early symmetry-based HIV protease inhibitors (Erickson et al., 1990; Kempf et al., 1990), poor oral bioavailability of terminal residue-substituted new compounds (Kempf et al., 1991), as well as the presence of protease inhibitor-resistant variants of HIV in untreated and treated patients (Condra et al., 1995; Lech et al., 1996) have made it necessary to search for other drugs with mechanisms of action that may differ from those of classical nucleoside analogs and protease inhibitors. Particularly, plant products have now attracted attention as possible anti-HIV drugs (Hudson and

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Towers, 1991; Lai et al., 1990; Balzarini et al., 1992; Skinner and Ezra, 1993; Ho and Li, 1993; Aruoma et al., 1996; Yamasaki et al., 1998; Vlietinck et al., 1998; Matthee et al., 1999; Min et al., 2001). We have now studied the in vitro anti-HIV activities of five plants found in Ghana.

2. Materials and methods

2.1. Drugs and plant extracts

AZT was purchased from Sigma, St. Louis, MO, USA. *Ocimum gratissimum* (GHX-2) and *Clausena anisata* (GHX-7) were collected based on their traditional uses against herpes zoster and herpes simplex virus infections. *Ficus polita* (GHX-6), *Alchornea cordifolia* (GHX-26), and *Elaeophorbia drupifera* (GHX-27) were randomly selected for testing. Twenty-five other plants were tested but these proved negative for anti-HIV activities. All plants were collected between March and April in the southern part of Ghana and were identified by D.K. Abbiw, Director of the Herbarium, Department of Botany, University of Ghana, Legon, Ghana. Aqueous extracts were prepared by boiling cut leaves (L), seeds (S), fruits (F), stems (ST), barks (B), and roots (R) in distilled water for about 10 min in conical flasks. The water extracts were centrifuged at 1500 rpm for 10 min and the supernatants were filtered through Whatman filter papers (Whatman Laboratory Division, Springfield Mill, UK). The filtrates were then freeze-dried.

2.2. Cell cultures and viruses

Molt-4 clone 8 and M8166 cells and HIV-1 strain $HTLVIII_B$ were provided by Professor M. Hayami, Institute for Virus Research, Kyoto University, Japan. HIV-1[GH3] was isolated from a Ghanaian AIDS patient (unpublished results). HIV-2[GH1] was isolated from a Ghanaian AIDS patient who had practiced prostitution in the Ivory Coast (Ishikawa et al., 1988). The chronically HIV-1 ($HTLVIII_B$)-infected Molt-4 cell line (Molt-4/HIV) was cloned in this laboratory. Cell medium and culture conditions were similar to previous work (Ayisi et al., 1991; Ayisi, 1995).

2.3. Antiviral and cytotoxicity assays in acute infection

The modified tetrazolium-based (MTT-based) colorimetric method was used to determine the susceptibility of HIV to inhibition by drugs. Drug controls included in the assays were used to determine the cytotoxicities of drugs. The method was similar to what is already published (Ayisi et al., 1991; Ayisi, 1995, 1998). In Molt-4 and M8166 cells, 50 μl of virus and 50 μl of 1.6×10^6 cells per milliliter were added to appropriate wells of poly-L-lysine coated 96-well microtitre plates. After various periods of virus infection, 100 μl of plant extracts or drug were added. After 5 days of incubation, the MTT-based assay was performed and the 50 and 90% effective concentrations (EC_{50} and EC_{90}) as well as 50% cytotoxic concentration (CC_{50}) were determined as previously published (Ayisi et al., 1991). Each experiment contained three replicates per treatment and was done twice. Plant extracts with anti-HIV activities were then selected and the experiments repeated two more times. The values given in this paper are, therefore, the averages of four determinations.

2.4. Inhibition of Molt-4 and Molt-4/HIV cell replication

Molt-4 and Molt-4/HIV cells were washed twice with growth medium. The cells were then counted by the trypan blue exclusion method and 4 ml of 3×10^5 of each cell type per milliliter were added to wells of six-well plates containing various concentrations of plant extracts. After 2 and 4 days of incubation, the cells were recounted by the trypan blue exclusion method.

2.5. Molt-4–Molt-4/HIV cocultures

Uninfected Molt-4 cells and Molt-4/HIV cells were cocultured in the presence of plant extracts or AZT in 96-well microtitre plates. Briefly, the cells were washed twice in growth medium and counted. They were then mixed at a ratio of 1:10 (infected:uninfected), and 100 μl of 3×10^5 mixed cells per milliliter were added to the respective wells. Corresponding drug control wells contained drugs and uninfected cells. After 12 h of incubation, the cultures were examined for HIV-1 cytopathicity (CPE) and the percentage CPE of control for each treatment was recorded. After 5 days of incubation, the MTT test was performed and the EC_{50} and EC_{90} concentrations determined. Each experiment was done twice and the averages of two determinations were recorded.

2.6. HIV reverse transcriptase (RT) assay

The effects of plant extracts on RT activity in vitro were evaluated with recombinant HIV-1 enzyme (Sekagaku Co., Tokyo, Japan) as described previously (Nakashima et al., 1992) except that the reaction mixture contained 5 μl of test plant extract or distilled water. The assays were carried out in triplicate.

2.7. Polymerase chain reaction studies

The effect of plant extracts on HIV proviral DNA co... (HIV proviral DNA-dependent synthesis by taq polym... was studied. DNA from HIV-1[$HTLVIII_B$] infected M... cells was extracted, amplified, and detected as previ... published (Ayisi et al., 1995), except that amplificati... done in the presence or absence of plant extracts.

3. Results

3.1. Comparative inhibitory effects of plant extracts and AZT against cytopathic effects of HIV-1 and HIV-2 acute infections in Molt-4 cells

Table 1 shows AZT to be extremely effective against HIV-1 strain $HTLVIII_B$ when treatment was started shortly after initiation of infection. Despite the fact that the plant extracts were not pure compounds, the antiviral indices of GHX-2L and GHX-2S were quite good. GHX-6L, GHX-26F, and GHX-27L had moderate anti-HIV indices and GHX-7L was mildly effective. Table 2A shows the effects of plant extracts and AZT tested against HIV-2 strain GH1, when treatment was started at 40 min after infection. With the exception of GHX-26, all plant extracts, particularly GHX-27L, were effective against HIV-2 strain GH1. When treatment was delayed to 2 h post-infection (Table 2B), the plant extracts (except for GHX-7L), were still able to achieve EC_{90} values that were not toxic to Molt-4 clone 8 cells. AZT was not able to achieve 90% inhibition of HIV-2 cytopathicity when treatment was delayed till 2 h post-infection.

3.2. Effects of multiplicity of infection on activities of plant extracts and AZT against HIV-1

Fig. 1 shows the effects of two plant extracts and AZT on HIV-1 strain GH3 at four different multiplicities of infection when treatment was delayed for 2 h. GHX-2L and GHX-6L had similar high to moderate concentration-dependent effects at the four multiplicities of infection. Both plant extracts were able to attain 90% cell protection even at the highest multiplicity of infection (MOI) of 0.114. AZT was very effective except when the MOI was increased to 0.114, under these conditions, 90% cell protection was never attained. The effectiveness of the plant extracts and AZT were inversely related to the MOI.

Table 1
Effects of aqueous extracts of plants against HIV-1 (strain $HTLVIII_B$) in Molt-4 clone 8 acutely infected at an MOI of 0.00357

Plant extract	EC_{50} (mg/ml)	CC_{50} (mg/ml)	AI
GHX-2L	0.01	1.1	110.0
GHX-6L	0.03	1.3	43.3
GHX-7L	0.70	>1.4[a]	≫2.0
GHX-26S	0.02	>1.8[a]	>90.0
GHX-26F	0.01	0.18	18.0
GHX-26S+F	0.01	0.71	71.0
GHX-27L	0.014	0.45	32.0
AZT	<0.000002	0.02	10000.0

Drug treatment was started at 40 min after virus infection. EC_{50}, 50% effective concentration; CC_{50}, 50% cytotoxic concentration; AI, antiviral index defined as CC_{50}/EC_{50}.
[a] Highest concentration tested.

Table 2
Effects of aqueous extracts of plants against HIV-2 (strain GH1) acute infection in Molt-4 clone 8 cells

	Plant extract	EC_{50} (mg/ml)	EC_{90} (mg/ml)	AI
A	GHX-2L	0.075	0.21	14.7
	GHX-2R	0.065	0.15	15.4
	GHX-6L	<0.005[a]	0.17	>260.0
	GHX-7L	0.110	0.40	12.7
	GHX-26S	NE		
	GHX-26F	NE		
	GHX-27L	<0.005[a]	0.02	>90.0
	AZT	<0.0000003[a]	0.0003	>66667.0
B	GHX-2L	0.13	0.32	
	GHX-2R	0.08	0.27	
	GHX-6L	0.025	0.40	
	GHX-7L	0.12	1.25	
	GHX-27L	0.008	0.03	
	AZT	0.000001	NE	

MOI was 0.018, and treatment was started after 40 min (A) or 2 h (B) of virus infection. NE, not effective; AI, antiviral index defined as CC_{50}/EC_{50}.
[a] Lowest concentration tested.

3.3. Comparative effects of plant extracts on the replication of uninfected and chronically infected Molt-4 cells

Fig. 2 shows the effect of plant extract GHX-27L on uninfected and chronically infected Molt-4 cells after treatment for 2 and 4 days. Whereas GHX-27L was toxic to uninfected cells at 0.28 mg/ml, as little as 0.035 mg/ml of this extract was significantly toxic to chronically infected cells. In fact, GHX-27L significantly reduced cell number below pretreatment levels indicating that it did not just stop or inhibit cell replication but in fact it killed the cells. Similar experiments showed that GHX-2L (up to 0.35 mg/ml) and GHX-6L (up to 0.64 mg/ml) did not affect Molt-4 and Molt-4/HIV growth, and that GHX-26F was significantly toxic to both uninfected and chronically infected cells at 0.16 mg/ml.

3.4. Effects of AZT and plant extracts on Molt-4–Molt-4/HIV cocultures

Fig. 3 shows the effects of AZT and plant extracts on cytopathic effects (CPE) observed in cocultures of Molt-4 with Molt-4/HIV after 12 h of incubation. Supernatant taken from 12-h-old untreated cultures did not contain enough virus to produce CPE in fresh Molt-4 cultures within 12 h. AZT had no effect on the CPE produced in the cocultures of Molt-4 with Molt-4/HIV at 12 h of incubation. All the plant extracts tested, on the other hand, showed concentration-dependent inhibition effects. Table 3 shows the results of tetrazolium-based colorimetric assay done after 5 days of incubation. Unlike the plant extracts, AZT was not able to achieve 90% cell protection.

3.5. Effects of plant extracts on HIV-1 reverse transcriptase activity

Fig. 4 shows the anti-HIV-1 RT activities of four plant extracts tested. All plant extracts showed concentration-

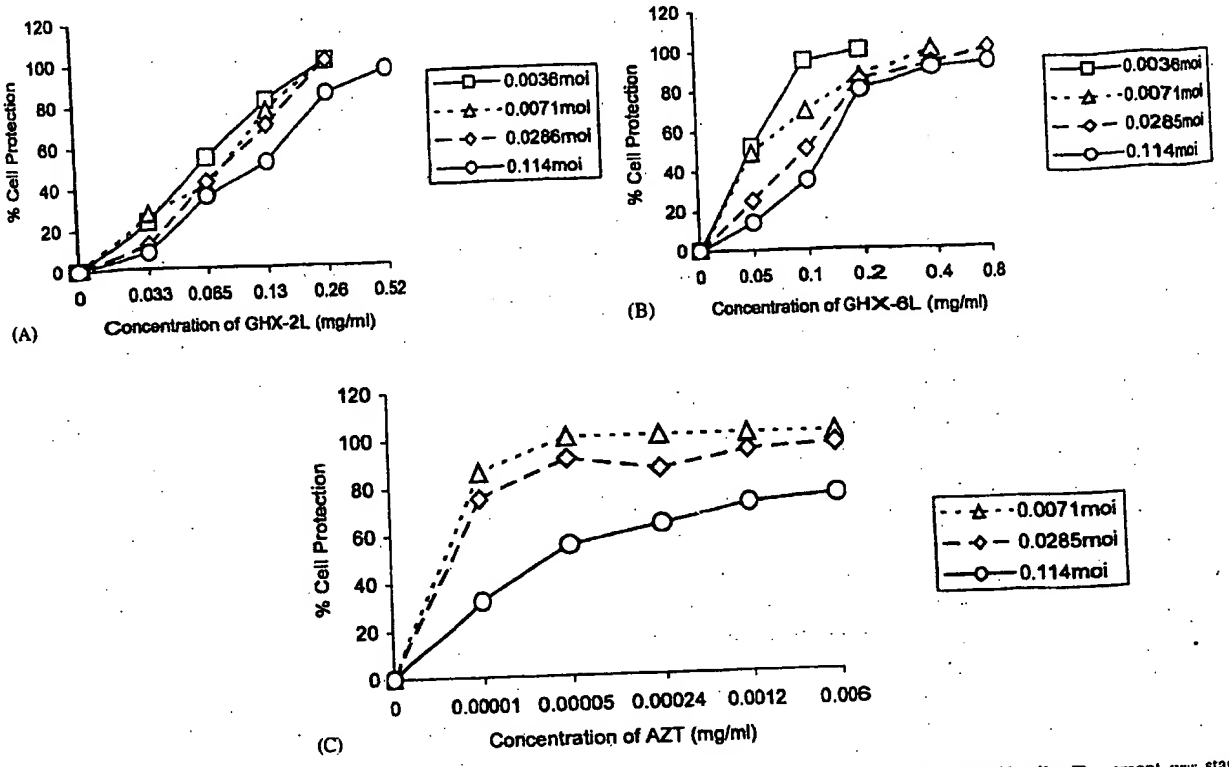

Fig. 1. Effects of MOI on anti-HIV-1 (strain GH3) activities of GHX-2L (A), GHX-6L (B), and AZT (C) in M8166 cells. Treatment was started at post-infection.

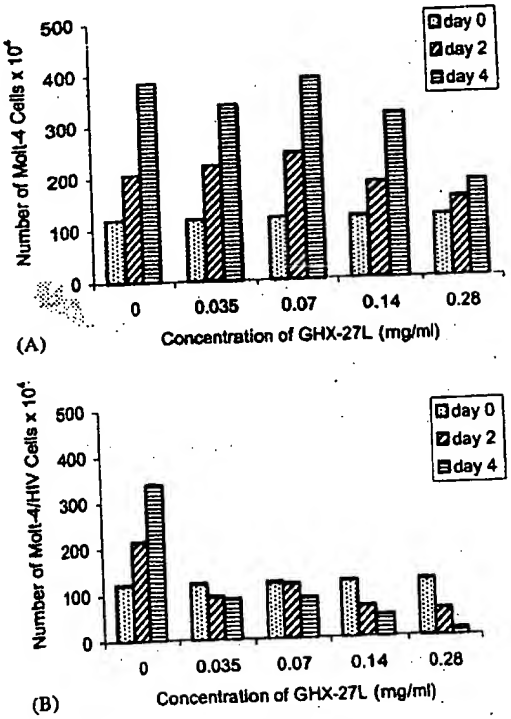

Fig. 2. Effects of plant extract GHX-27L on Molt-4 (A) and Molt-4/HIV (B) cell growth.

Table 3
Effects of AZT and plant extracts GHX-2L, GHX-6L, GHX-26F, and GHX-27L on cocultures of Molt-4 with Molt-4/HIV after 5 days of incubation

Plant extract or drug	EC_{50} (mg/ml)	EC_{90} (mg/ml)
GHX-2L	0.059	0.340
GHX-6L	0.018	0.130
GHX-26F	0.035	0.126
GHX-27L	0.013	0.075
AZT	0.001	NE[a]

The highest cell protection by AZT was 55% at a concentration of 0.005 mg/ml.
[a] NE, not effective.

dependent reductions in RT activity. GHX-2L, GHX-6L and GHX-26F caused 90% reduction in HIV-1 RT activity at concentrations between 0.013 and 0.020 mg/ml. On the other hand, GHX-27L was not able to cause 90% reduction in RT activity even at the highest concentration of 0.133 mg/ml tested.

3.6. Effects of plant extracts on HIV-1 proviral DNA copying

GHX-2L and GHX-6L were able to stop in vitro HIV-1 proviral DNA copying by taq polymerase at concentrations of 0.011 and 0.015 mg/ml, respectively. A faint band

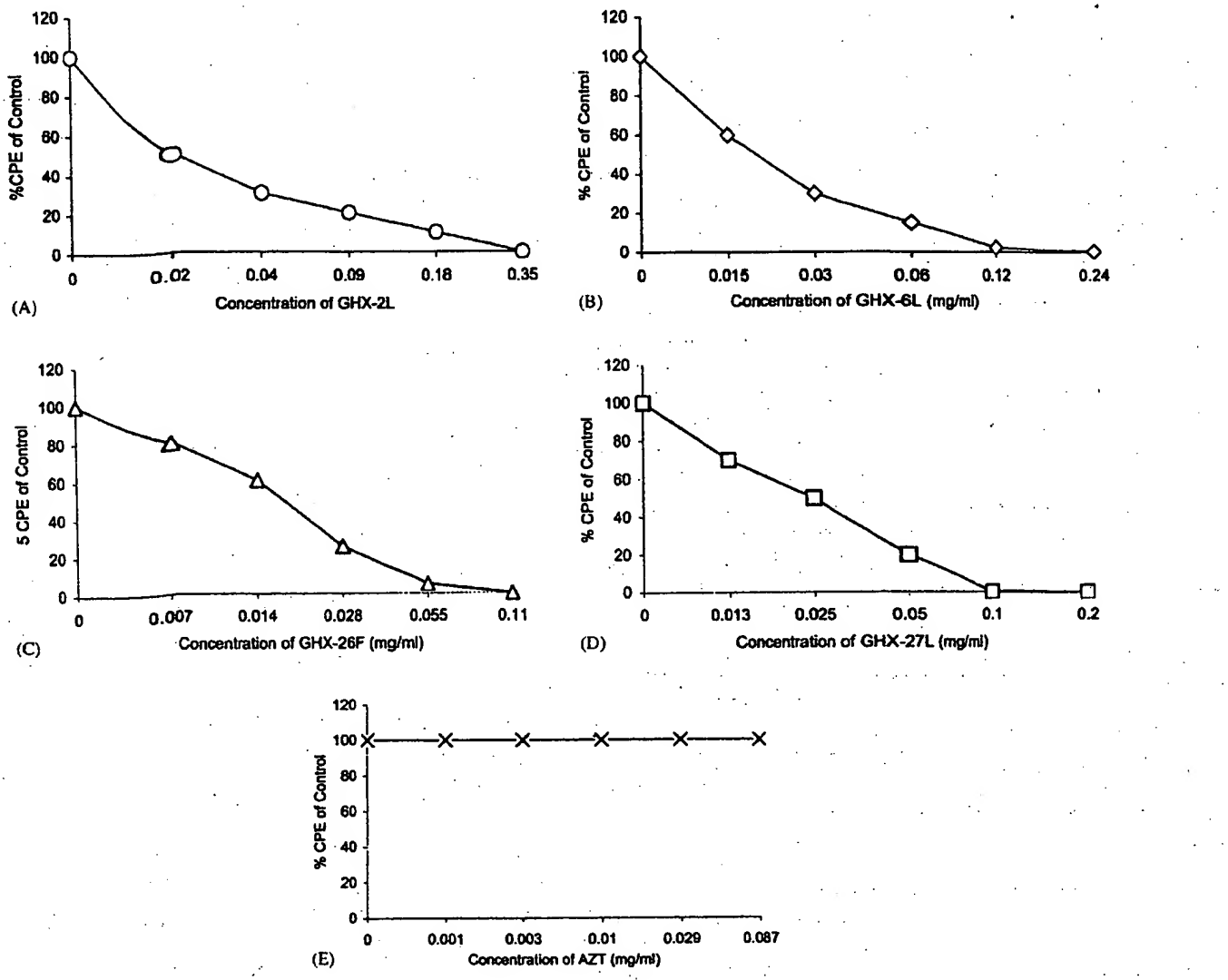

Fig. 3. Effects of GHX-2L (A), GHX-6L (B), GHX-26F (C), GHX-27L (D), and AZT (E) on the cytopathicity in Molt-4 cocultures with Molt-4/HIV after 12 h incubation.

HIV-1 DNA copy band was present for GHX-26F and GHX-27L at 0.016 and 0.058 mg/ml, respectively. Plant extracts GHX-7L and GHX-26S had no effect on HIV-1 DNA-dependent DNA synthesis.

4. Discussion

One of the modes of infection by HIV is acute cytolytic infection. The fact that all five plant extracts had noncytotoxic activities against acute HIV infection indicates that these extracts are acting as true antivirals. This fact is emphasized by the demonstration of MOI-dependent activities, exemplified by GHX-2L and GHX-6L. Virus production in HIV-infected patients is usually high (Pantaleo et al., 1993; Embretson et al., 1993; Wei et al., 1995; Ho et al., 1995), resulting in high in vivo MOI. At low MOI, AZT and plant extracts GHX-2L and GHX-6L were able to achieve 90% inhibition of HIV-1 even when treatment was delayed for 2 h. AZT, unlike the plant extracts, was not able to achieve 90% inhibition of HIV-1 at high MOI under similar conditions.

Despite the predominance of HIV-1 worldwide, a low incidence of HIV-2 and a moderate incidence of dual infection exists in West Africa (Hishida et al., 1994; Ayisi et al., 1995). All plants tested, except for GHX-26, were effective against HIV-2 strain GH1 demonstrating the potential usefulness of these plants in the area where they were collected. At 40 min post-infection, it is expected that adsorption and penetration would have been completed with very little DNA synthesis if any. The ineffectiveness of AZT in achieving considerable viral inhibition against HIV-2 when treatment was started at 2 h post-infection is not surprising since this

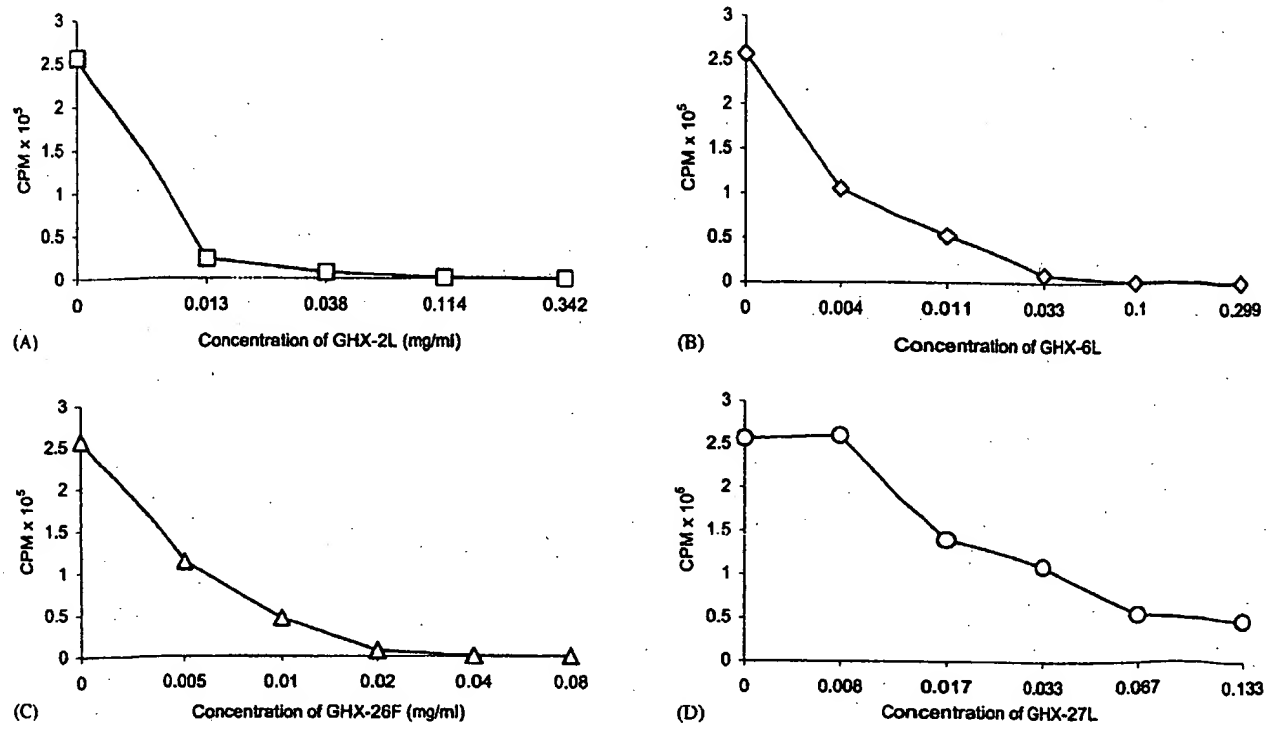

Fig. 4. Effects of GHX-2L (A); GHX-6L (B); GHX-26F (C); and GHX-27L (D) on HIV RT activity.

drug acts only on the early event of RT activity. AZT was, however, very effective against HIV-1 at a similar, low MOI as used for HIV-2. This difference in activity may be due to differences in the rates of HIV-1 and HIV-2 proviral DNA synthesis and integration. This difference in activity is obviated when high MOI of HIV-1 is used. The plant extracts, however, achieved considerable HIV inhibition irrespective of the MOI used and may be active against late viral events.

Several stages of HIV replication serve as targets for drugs (Tuazon and Labriola, 1987; Wong-Staal, 1990). Early events in HIV infection are critical targets because of the role of the RT enzyme, which is unique to this virus and a few others and not found in uninfected cells. This unique enzyme characterizes a two-step process of proviral DNA synthesis (Coffin, 1990). Unintegrated proviral DNA is metabolically active and plays a critical role in the cytopathicity of HIV (Stevenson et al., 1990). Thus, drugs that inhibit RT activity should be beneficial against acute HIV infections. AZT is a known potent inhibitor of both steps of RT activity (Wong-Staal, 1990). GHX-2L and GHX-6L showed consistent high activities against HIV-1 RT in the synthesis of DNA from RNA template (first step) and also inhibited proviral DNA copying by taq polymerase (proviral DNA-dependent DNA synthesis) and thus the two steps in early HIV replication may serve as possible targets for these extracts. GHX-26F while being very effective against RNA-dependent DNA synthesis, was less effective against proviral DNA-dependent DNA synthesis and may have its major activity at RT at the first step. Despite the concentration-dependent anti-RT activities for the tested extracts, this enzyme may not be the primary target for their anti-HIV activities since inhibition of viral cytopathicity was achieved even when treatment was started after proviral DNA synthesis.

When uninfected Molt-4 cells are cocultured with chronically HIV-1-infected Molt-4 cells (Molt-4/HIV), the first sign of HIV cytopathicity was seen within 8–12 h. This is probably due to fusion of uninfected with infected cells. At this stage, not enough virus particles could have been produced by the chronically infected cells to cause such clear cytopathicity within such a short time. In fact, acute HIV-1 infection in Molt-4 cells will take about 72 h for the first clear cytopathicity to be discernible. Thus, the cytopathicity observed within 8–12 h is likely not due to HIV-1 acute infection. This point is further strengthened by the fact that AZT had no effect on this early cytopathicity. The inhibition of this early cytopathicity in uninfected–infected coculture indicates yet another mode of anti-HIV action by the plant extracts. A unique effect on chronically infected cells was observed for plant extract GHX-27L. This extract was selectively toxic to chronically infected cells and thus provides evidence of the possibility of developing drugs with the ability to shut off the virus producing factories by being selectively toxic to chronically infected cells. The fact that GHX-27L significantly reduced chronically infected cell number below pretreatment levels indicates that this extract did not just stop or inhibit cell replication but that in fact it killed the cells. The mechanism underlying the selectiv-

killing of chronically infected cells is unknown but may be due to possible differential uptake of the extract into uninfected and chronically infected cells. This hypothesis will be investigated in future experiments.

Even though the anti-HIV components of the plant extracts have not been studied, phytochemistry work by others shed light on the nature of possible active ingredients for some of them. Eugenol (Nakamura et al., 1999; de Vasconcelos Silva et al., 1999) and thymol (Rodriguez et al., 1997), two phenolic compounds, were found to be antibacterial components of *O. gratissimum*. Ebi (2001) found fractionation components of *A. cordifolia* containing phenolics and terpenoids to have significant antibacterial activities. Even though no phytochemistry has been reported for *F. polita*, other *Ficus* species have been shown to contain various potential antiviral compounds. *Ficus pumila* contains triterpenoids (Kitajima et al., 1998), acetylated triterpenoids (Kitajima et al., 1999), and sesquiterpenoid glucosides (Kitajima et al., 2000). Furanocoumarins, sesquiterpene hydrocarbons, and oxygenated sesquiterpenes have also been isolated from *Ficus carica* (Gibenau et al., 1997). Baumgartner et al. (1990), Khan et al. (1993) isolated alkaloids from *Ficus septica* and *Ficus pachythachis*, respectively. Likewise, even though no phytochemistry has been done for *E. drupifera*, other species of *Euphorbia* have been shown to contain potential anti-HIV compounds. Uemura and Hirata (1971, 1972, 1974) discovered new diterpenoids from *Euphorbia jolikini* (1972) and *Euphorbia kansui Liou* (1974), 13-oxyingenol from *E. Kansui Liou* (1974), and two new alkaloids from *Euphorbia millii* (1971). Cycloeuphordenol, a new triterpene was isolated from *Euphorbia tirucalli* (Khan et al., 1988). Lectins (Lynn and Clevette, 1986) and tannins (Yoshida et al., 1994) have also been isolated from *Euphorbia* species. Ito et al. (1998) isolated the first lactone carbazole alkaloids from a natural source, *C. anisata*. Some phenolics may inhibit HIV adsorption and integration, some terpenoids may inhibit HIV adsorption, virus–cell fusion, and reverse transcription, some alkaloids may inhibit HIV adsorption, reverse transcription and glycosylation, and some coumarins may inhibit HIV adsorption, reverse transcription, integration, protease and assembly/release, some lectins may inhibit HIV–cell fusion, and some tannins may inhibit HIV adsorption and reverse transcription (Vlietinck et al., 1998; Matthee et al., 1999).

In this paper, we showed that aqueous extracts of *O. gratissimum* (GHX-2), *F. polita* (GHX-6), *C. anisata* (GHX-7), *A. cordifolia* (GHX-26), and *E. drupifera* (GHX-27) are effective inhibitors of HIV-1 and HIV-2 replication. The plant extracts unlike AZT were able to achieve significant inhibition of viral cytopathicity even at high MOI when treatment was delayed for 2 h. Early fusion of chronically HIV-infected cells with uninfected cells has been shown to be unaffected by AZT but to be inhibited by GHX-2, GHX-6, GHX-26, and GHX-27. Significantly, an extract of *E. drupifera* has been identified to be selectively toxic to chronically infected cells at concentrations that are not toxic to uninfected cells. In order to further delineate their therapeutic potentials in clinical HIV infections/AIDS, the plant extracts will have to be tested against other strains of HIV-1 and -2, including those that are resistant to AZT.

Acknowledgements

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United States Court of Customs and Patent Appeals.
Application of Alfred MARZOCCHI and Richard C. Horton.
Patent Appeal No. 8431.

April 15, 1971.

Appeal from decision of the patent office board of appeals which affirmed final rejection of claims 5, 6, 11 and 12 of application, serial No. 470,618, involving technique for improving adhesion characteristics between glass fibers and vinyl polymer resins. The Court of Customs and Patent Appeals, Baldwin, J., held that claims 5 and 11, teaching use of monomeric vinyl pyrrolidone, were obvious in light of reference teaching use of polymeric vinyl pyrrolidone, but that claims 6 and 12, reciting use of polyethyleneamine, were supported by disclosure which was in compliance with requirements of specification statute despite the breadth of the claim, where record contained insufficient grounds for questioning the accuracy of teaching that any polyethyleneamine would function to accomplish the asserted result.

Affirmed in part and reversed in part.

West Headnotes

[1] Patents 16.4
291k16.4 Most Cited Cases
(Formerly 291k18)
In connection with patent application involving technique for improving adhesion characteristics between glass fibers and vinyl polymer resins, claims 5 and 11, teaching use of monomeric vinyl pyrrolidone were obvious in light of reference teaching use of polymeric vinyl pyrrolidone. 35 U.S.C.A. § 103.

[2] Patents 16(3)
291k16(3) Most Cited Cases
(Formerly 291k18)
Inference of fact that, to one possessing the ordinary level of skill in the art, it would be obvious to try particular composition may at times be enough to justify drawing the ultimate conclusion of law that the claimed subject matter as a whole would have been obvious. 35 U.S.C.A. § 103.

[3] Patents 101(4)
291k101(4) Most Cited Cases
Claims 6 and 12 of patent application relating to technique for improving adhesion characteristics between glass fibers and vinyl polymer resins, which recited use of "polyethyleneamine" were supported by disclosure which was in compliance with specification statute despite contention as to excessive breadth of the disputed term, where record contained insufficient grounds for questioning accuracy of teaching that any polyethyleneamine would function to accomplish the asserted result. 35 U.S.C.A. § 112.

[4] Patents 101(4)
291k101(4) Most Cited Cases
Where generic term is recited in patent application, the only relevant concern of the patent office under specification statute should be the truth of the assertion that any member of the class will accomplish the desired result, not the breadth of the term. 35 U.S.C.A. § 112.

[5] Patents 101(4)
291k101(4) Most Cited Cases
Specification disclosure which contains teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the specification statute unless there is reason to doubt the objective truth of statements contained in the specification which must be relied on for enabling support. 35 U.S.C.A. § 112.

[6] Patents 113(7)
291k113(7) Most Cited Cases
Unpredictability of chemical reactions alone may be enough to create reasonable doubt as to accuracy of particular broad statement put forward as enabling support for claim, especially where the statement is, on its face, contrary to generally accepted scientific principles, but it is incumbent upon the patent office, when rejection is made on this basis, to explain why it doubts the truth or accuracy of the statement. 35 U.S.C.A. § 112.

[7] Patents 101(4)
291k101(4) Most Cited Cases
In considering accuracy of specification, pertinent references are not necessarily prior art references. 35 U.S.C.A. § 112.

Patents 328(2)
291k328(2) Most Cited Cases
2,853,465. Cited as reference.
****221 *1069** Herman Hersh, McDougall, Hersh, Scott & Ladd, Chicago, Ill., attorney of record, for appellant. Staelin & Overman, Toledo, Ohio, George A. Degnan, Arlington, Va., of counsel.

S. Wm. Cochran, Washington, D.C., for the Commissioner of Patents. Fred W. Sherling, Washington, D.C., of counsel.

***1070** Before RICH, ALMOND, BALDWIN and LANE, Judges, and DURFEE, Judge, United States Court of Claims, sitting by designation.

BALDWIN, Judge.

This is an appeal from the decision of the Patent Office Board of Appeals which affirmed the final rejection of claims 5 and 11 of appellants' application [FN1] under 35 U.S.C. § 103 as unpatentable in view of Werner [FN2] and of claims 6 and 12 under 35 U.S.C. § 112 as being based on an inadequate disclosure. Claims 4 and 10 stand allowed.

> FN1. Serial No. 470,618, filed July 8, 1965, for 'Fiber Coatings-- Nitrogen Compounds for Improving Adhesion of Vinyl Polymers to Glass' as a continuation-in-part of Serial No. 96,106, filed March 16, 1961.
>
> FN2. U.S. Patent No. 2,853,465, issued September 23, 1958.

THE INVENTION

The subject matter of the claims on appeal involves a technique for improving the adhesion characteristics between glass fibers and vinyl polymer resins. Claim 5 is representative and reads as follows:

5. In the combination of glass fibers and a vinyl polymer resin composition present as a coating on the glass fiber surfaces, the improvement which comprises mixing the vinyl polymer resin, prior to coating of the glass fibers, with an amine compound in an amount corresponding to 2-10% By weight of the vinyl polymer resin, and in which the amine compound is monomeric vinyl pyrrolidone.

Claim 11 is drawn to the same concept as claim 5, but defines the invention as 'a method of producing glass fibers coated with polyvinyl resin strongly bonded to the glass fiber surfaces.' Claims 6 and 12 differ from claims 5 and 11 respectively solely in the recitation of 'polyethyleneamine' as the critical 'amine compound' additive.

THE SECTION 103 REJECTION

Claims 5 and 11 were rejected 'as obvious in the sense of 35 USC 103 over Werner.' Werner, the sole reference relied upon here, is addressed to the improvement in the bonding relationship between glass and polyvinyl halide resins. The pertinent disclosure is as follows:

I have found that polyvinyl halide resins may be successfully modified so as to obtain excellent glass adhesion by employing a mixture of a polyvinyl halide and a polymer of N-vinyl pyrrolidone. By employing a mixture containing from 80 to 97% Of a polyvinyl halide and from 20 to 3% Of a polymer of N-vinyl pyrrolidone, which term includes homopolymers of vinyl pyrrolidone and copolymers with other polymerizable monomers, a composition is obtained having extremely high adhesion to all glass surfaces.

***1071** On the basis of this teaching the examiner took the position, accepted by the ****222** board, that the claimed use of monomeric vinyl pyrrolidone rather than Werner's polymeric vinyl pyrrolidone would be obvious to one of ordinary skill in the art since Werner's teaching would indicate to 'one skilled in the art * * * that it is the vinyl pyrrolidone moiety that is enhancing the adhesion.' It was also suggested by the examiner that since the claims recite no temperature conditions for the coating operation and since monomers polymerize when heated, the claims could possibly cover circumstances wherein the monomer is polymerized during application. The board appears to have accepted this suggestion and to have extended it even further. It stated:

All of Werner's examples specify heating at elevated temperatures (110 degrees C.-130 degrees C., 165 degrees C., 325 degrees F., 350 degrees F) with and without elevated pressures. Appellants' specification says nothing about retaining the vinyl pyrrolidone in monomeric form, much less anything about 'maximizing adhesion' by preventing polymerization. Indeed, the very designation of the vinyl pyrrolidone as a 'monomeric' material introduced into a polymer system for the purpose of altering the properties of such system implies subsequent polymerization of the monomer. Appellants' further argument that the monomer has entirely different capabilities and

solubilities than the polymer is also unpersuasive.

Appellants' position on appeal in response to these assertions by the examiner and board is largely to stress again the 'marked difference between the properties and characteristics of a polymer as compared to a monomer,' and to object to the 'purely conjectural' assertion that the monomer polymerizes in the coating after it is applied. Additionally, appellants make the following contention:

Even if it were assumed that appellants' monomeric vinyl pyrrolidone is polymerized when present in the polyvinyl chloride coating, there is no teaching or suggestion in Werner that the use of monomeric vinyl pyrrolidone has any efficacy whatsoever in compositions of the type disclosed and claimed. The basis suggested by the Patent Office for the rejection is tantamount to the allegation it would be 'obvious to try' the monomer. This 'test' of obviousness has been frequently repudiated by this court.

[1] The sole issue is, of course, whether the Werner teaching does suggest to a person having ordinary skill in this art that the use of monomeric vinyl pyrrolidone would have the efficacy indicated in the appealed claims. We agree with appellants that whether the monomer polymerizes is irrelevant, at least in this regard. What is relevant, however, and here determinative, is the examiner's assertion that the Werner teaching would suggest that it is the vinyl pyrrolidone moiety alone and not some other characteristic peculiar to a polymer which is efficacious in producing the desired adhesion enhancement. ***1072** [FN3] In the absence of anything to rebut this assertion, which is reasonable on its face, we are constrained to accept it as fact. The inferences which follow from such fact, i.e., that the monomer would possess this same characteristic and that one of ordinary skill would recognize such fact, are inescapable.

> FN3. Indeed, the reasonableness of such an assertion is confirmed by the very disclosure contained in appellants' application which indicates that efficacious adhesion enhancers are those 'organic nitrogenous compounds which are characterized both by an organic constitution which is compatible with the vinyl polymers and by a polarity expressed in the nitrogen function.' As also pointed out by appellants in their brief (about which more will be said later), the nature of the present invention resides in the use of amine compounds, broadly, as adhesion enhancers.

[2] It is acknowledged that the above line of reasoning may be viewed as being tantamount to drawing the inference that, to one possessing the ordinary level of skill in this art, it would be 'obvious ****223** to try' the monomer. Nevertheless, such an inference of fact may, at times, be enough to justify drawing the ultimate conclusion of law that the claimed subject matter as a whole would have been obvious under section 103. We are satisfied that the circumstances of this case justify an initial conclusion of obviousness. Since the record before us contains nothing to rebut that conclusion, the decision with regard to claims 5 and 11 must be affirmed.

THE SECTION 112 REJECTION

Claims 6 and 12, which recite the use of 'polyethyleneamine' as the adhesion enhancer, were criticized by the examiner as being based on a disclosure which was not enabling under the first paragraph of 35 U.S.C. § 112. The board affirmed his rejection of those claims with the following comment.

The term is obviously generic to a considerable number of compounds varying in the number of ethylene groups, the number of amine groups and the relationship of the polyethylene groups to the amine groups, and accordingly does not provide a reasonable guide for those seeking to improve the adherence of vinyl resins to glass.

[3] We will reverse the board's decision on this rejection since we are unable to find sufficient justification for the holding that appellants' disclosure is not enabling.

[4] Turning specifically to the objections noted by the board as indicated above, it appears that these comments indicate nothing more than a concern over the breadth of the disputed term. If we are correct, then the relevance of this concern escapes us. It has never been contended that appellants, when they included the disputed term in their specification, intended only to indicate a single compound. Accepting, therefore, that the term is a generic one, its recitation must be taken as an assertion by appellants that all of the 'considerable ***1073** number of compounds' which are included within the generic term would, as a class, be operative to produce the asserted enhancement of adhesion characteristics. The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of § 112 requires

nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

[5] As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling.

[6][7] In the field of chemistry generally, there may be times when the wellknown unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, [FN4] will be available to substantiate any doubts that the asserted scope of objective enablement ****224** is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure. Cf. In re Gazave, 379 F.2d 973, 54 CCPA 1524 (1967); In re Chilowsky, 229 F.2d 457, 43 CCPA 775 (1956).

> FN4. Not necessarily prior art references, it should be noted, since the question would be regarding the accuracy of a statement in the specification, not whether that statement had been made before.

In the present case, the circumstances we see do not support the reasonableness of any doubts which the Patent Office might have had ***1074** concerning the adequacy of appellants' specification disclosure to support these claims. In fact, those circumstances tend to strengthen rather than weaken appellants' claim to the breadth of protection they seek. In the first place, it has not been asserted by the Patent Office that the chemical properties of known polyethyleneamines vary to such an extent that it would not be expected by one of ordinary skill in this art that any such compound would possess the necessary capability of enhancing adhesion. Additionally, we note that polyethyleneamine is listed in appellants' specification as being only one of a much larger class of amine compounds possessing this necessary characteristic. Finally, we recognize (as did the examiner) the generic nature of appellants' broader concept, i.e., that the desired property of adhesion enhancement stems largely from the amine moiety. It does appear that variation of certain of the secondary factors mentioned by the examiner, such as molecular weight or proportion of ethylene groups, might influence to some degree or even mask the essential 'amine' property of the polyethyleneamine or its obviously equally essential compatibility with vinyl polymers. However, we see no basis to conclude that the ready avoidance of this result would not be within the level of ordinary skill in this art. Compare In re Skrivan, 427 F.2d 801, 57 CCPA 1201 (1970).

Taking all these circumstances into consideration, we are constrained to conclude that the record before us contains insufficient grounds for questioning the accuracy of appellants' teaching that any polyethyleneamine (obviously excepting those whose essential 'amine' characteristics and compatibility with vinyl polymers would be masked by the secondary factors mentioned) will function to accomplish the asserted result. It follows that claims 6 and 12 must be held to be supported by a disclosure which is in compliance with the requirements of the first paragraph of 35 U.S.C. § 112.

SUMMARY

The decision of the board regarding claims 5 and 11 is affirmed; that dealing with claims 6 and 12 is reversed.

***1069** Modified.

58 C.C.P.A. 1069, 439 F.2d 220, 169 U.S.P.Q. 367

END OF DOCUMENT

▷

Briefs and Other Related Documents

United States Court of Appeals,
Federal Circuit.
In re Jack R. WANDS, Vincent R. Zurawski, Jr., and Hubert J.P. Schoemaker.
No. 87-1454.

Sept. 30, 1988.

Inventors of method to create immunoassay of hepatitis B surface antigen using monoclonal antibodies sought patent. The Board of Patent Appeals and Interferences denied the patent on grounds it was not enabling. On appeal, the Court of Appeals, Edward S. Smith, Circuit Judge, held that: (1) determination of enablement is reviewed as question of law; (2) while deposit of living cells can be used to satisfy enabling requirement, it is not necessary; (3) undue experimentation was not necessary to produce art for method of immunoassay of hepatitis B surface antigen using monoclonal antibodies; and (4) enablement of patent involving living microorganisms is not precluded by necessity of some experiments such as routine screening.

Reversed.

Pauline Newman, Circuit Judge, concurred in part and dissented in part with opinion.

West Headnotes

[1] Patents 113(6)
291k113(6) Most Cited Cases
While facts underlying patent application as found by Board of Patent Appeals and Interferences are reviewed under clearly erroneous standard, enablement determination is reviewed as a question of law. 35 U.S.C.A. § 112.

[2] Patents 99
291k99 Most Cited Cases
Where an invention depends on use of living materials such as microorganisms or cultured cells, it may be impossible to enable the public to make the invention solely by means of a written disclosure; thus, enabling requirement can be met by deposit of living materials in cell depositories which will distribute samples to public who wish to practice the invention after the patent issues. 35 U.S.C.A. § 112.

[3] Patents 99
291k99 Most Cited Cases
Although inventions involving microorganisms or other living cells can be enabled by their deposit with cell depository, a deposit is not always necessary to satisfy the enablement requirement. 35 U.S.C.A. § 112.

[4] Patents 99
291k99 Most Cited Cases
No deposit of living cells is necessary to meet the enabling requirement of invention which involves microorganisms or other living cells if the biological organism can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation. 35 U.S.C.A. § 112.

[5] Patents 99
291k99 Most Cited Cases
Determination of whether specification in a patent application involving living cells is enabled without a deposit of cells is decided on facts of the particular case. 35 U.S.C.A. § 112.

[6] Patents 99
291k99 Most Cited Cases
Undue experimentation was not necessary to practice art of method for immunoassay of hepatitis B surface antigen using monoclonal antibodies and thus invention was enabling without deposit of living cells; successful and successive creation of antibodies was not undermined by four prior failures or inventors' lack of testing of other stored hybridomas created by method where cell fusion was technique well known to those of ordinary skill in monoclonal antibody art, and no claim was made that fusion step was more difficult or unreliable for any other antigen than antigen created by method. 35 U.S.C.A. § 112.

[7] Patents 99
291k99 Most Cited Cases
Enablement of patent involving living microorganisms is not precluded by necessity for some experimentation such as routine screening. 35 U.S.C.A. § 112.

[8] **Patents** 99
291k99 Most Cited Cases
Determination of whether undue experimentation is needed to reproduce an invention involving living microorganisms and demonstrate lack of enablement is not a single factual determination but a conclusion reached by weighing many factual considerations. 35 U.S.C.A. § 112.

[9] **Patents** 99
291k99 Most Cited Cases
Factors to be considered in determining whether a disclosure would require undue experimentation and undermine enabling requirement for patent involving living microorganisms due to lack of deposit of cells include quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of prior art, relative skill of those in the art, predictability of the art, and breadth of the claims. 35 U.S.C.A. § 112.

Patents 328(2)
291k328(2) Most Cited Cases
4,271,145. Cited.
***732** Jorge A. Goldstein, of Saidman, Sterne, Kessler & Goldstein, Washington, D.C., argued for appellant. With him on the brief was Henry N. Wixon, Washington, D.C.

John H. Raubitschek, Associate Sol., Com'r of Patents and Trademarks, of Arlington, Va., argued for appellee. With him on the brief were Joseph F. Nakamura, Sol. and Fred E. McKelvey, Deputy Sol., Washington, D.C.

Before SMITH, NEWMAN, and BISSELL, Circuit Judges.

***733** EDWARD S. SMITH, Circuit Judge.

This appeal is from the decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (board) affirming the rejection of all remaining claims in appellant's application for a patent, serial No. 188,735, entitled "Immunoassay Utilizing Monoclonal High Affinity IgM Antibodies," which was filed September 19, 1980. [FN1] The rejection under 35 U.S.C. § 112, first paragraph, is based on the grounds that appellant's written specification would not enable a person skilled in the art to make the monoclonal antibodies that are needed to practice the claimed invention without undue experimentation. We reverse.

FN1. *In re Wands,* Appeal No. 673-76 (Bd.Pat.App. & Int. Dec. 30, 1986).

I. *Issue*

The only issue on appeal is whether the board erred, as a matter of law, by sustaining the examiner's rejection for lack of enablement under 35 U.S.C. § 112, first paragraph, of all remaining claims in appellants' patent application, serial No. 188,735.

II. *Background*

A. *The Art.*

The claimed invention involves immunoassay methods for the detection of hepatitis B surface antigen by using high-affinity monoclonal antibodies of the IgM isotype. *Antibodies* are a class of proteins (immunoglobulins) that help defend the body against invaders such as viruses and bacteria. An antibody has the potential to bind tightly to another molecule, which molecule is called an *antigen.* The body has the ability to make millions of different antibodies that bind to different antigens. However, it is only after exposure to an antigen that a complicated *immune response* leads to the production of antibodies against that antigen. For example, on the surface of hepatitis B virus particles there is a large protein called *hepatitis B surface antigen* (HBsAg). As its name implies, it is capable of serving as an antigen. During a hepatitis B infection (or when purified HBsAg is injected experimentally), the body begins to make antibodies that bind tightly and specifically to HBsAg. Such antibodies can be used as regents for sensitive diagnostic tests (*e.g.,* to detect hepatitis B virus in blood and other tissues, a purpose of the claimed invention). A method for detecting or measuring antigens by using antibodies as reagents is called an *immunoassay.*

Normally, many different antibodies are produced against each antigen. One reason for this diversity is that different antibodies are produced that bind to different regions (determinants) of a large antigen molecule such as HBsAg. In addition, different antibodies may be produced that bind to the same determinant. These usually differ in the tightness with which they bind to the determinant. *Affinity* is a quantitative measure of the strength of antibody-antigen binding. Usually an antibody with a higher affinity for an antigen will be more useful for immunological diagnostic tests than one with a lower affinity. Another source of heterogeneity is that there are several immunoglobulin classes or *isotypes.* Immunoglobulin G (IgG) is the most common

isotype in serum. Another isotype, immunoglobulin M (IgM), is prominent early in the immune response. IgM molecules are larger than IgG molecules, and have 10 antigen-binding sites instead of the 2 that are present in IgG. Most immunoassay methods use IgG, but the claimed invention uses only IgM antibodies.

For commercial applications there are many disadvantages to using antibodies from serum. Serum contains a complex mixture of antibodies against the antigen of interest within a much larger pool of antibodies directed at other antigens. These are available only in a limited supply that ends when the donor dies. The goal of monoclonal antibody technology is to produce an unlimited supply of a single purified antibody.

The blood cells that make antibodies are *lymphocytes*. Each lymphocyte makes only one kind of antibody. During an immune response, lymphocytes exposed to ***734** their particular antigen divide and mature. Each produces a *clone* of identical daughter cells, all of which secrete the same antibody. Clones of lymphocytes, all derived from a single lymphocyte, could provide a source of a single homogeneous antibody. However, lymphocytes do not survive for long outside of the body in cell culture.

Hybridoma technology provides a way to obtain large numbers of cells that all produce the same antibody. This method takes advantage of the properties of *myeloma* cells derived from a tumor of the immune system. The cancerous myeloma cells can divide indefinitely in vitro. They also have the potential ability to secrete antibodies. By appropriate experimental manipulations, a myeloma cell can be made to fuse with a lymphocyte to produce a single hybrid cell (hence, a hybridoma) that contains the genetic material of both cells. The hybridoma secretes the same antibody that was made by its parent lymphocyte, but acquires the capability of the myeloma cell to divide and grow indefinitely in cell culture. Antibodies produced by a clone of hybridoma cells (i.e., by hybridoma cells that are all progeny of a single cell) are called monoclonal antibodies. [FN2]

> FN2. For a concise description of monoclonal antibodies and their use in immunoassay see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1368-71, 231 USPQ 81, 82-83 (Fed.Cir.1986), *cert. denied*, 480 U.S. 947, 107 S.Ct. 1606, 94 L.Ed.2d 792 (1987).

B. *The Claimed Invention.*

The claimed invention involves methods for the immunoassay of HBsAg by using high-affinity monoclonal IgM antibodies. Jack R. Wands and Vincent R. Zurawski, Jr., two of the three coinventors of the present application, disclosed methods for producing monoclonal antibodies against HBsAg in United States patent No. 4,271,145 (the '145 patent), entitled "Process for Producing Antibodies to Hepatitis Virus and Cell Lines Therefor," which patent issued on June 2, 1981. The '145 patent is incorporated by reference into the application on appeal. The specification of the '145 patent teaches a procedure for immunizing mice against HBsAg, and the use of lymphocytes from these mice to produce hybridomas that secrete monoclonal antibodies specific for HBsAg. The '145 patent discloses that this procedure yields both IgG and IgM antibodies with high-affinity binding to HBsAg. For the stated purpose of complying with the best mode requirement of 35 U.S.C. § 112, first paragraph, a hybridoma cell line that secretes IgM antibodies against HBsAg (the 1F8 cell line) was deposited at the American Type Culture Collection, a recognized cell depository, and became available to the public when the '145 patent issued.

The application on appeal claims methods for immunoassay of HBsAg using monoclonal antibodies such as those described in the '145 patent. Most immunoassay methods have used monoclonal antibodies of the IgG isotype. IgM antibodies were disfavored in the prior art because of their sensitivity to reducing agents and their tendency to self-aggregate and precipitate. Appellants found that their monoclonal IgM antibodies could be used for immunoassay of HbsAg with unexpectedly high sensitivity and specificity. Claims 1, 3, 7, 8, 14, and 15 are drawn to methods for the immunoassay of HBsAg using high-affinity IgM monoclonal antibodies. Claims 19 and 25-27 are for chemically modified (*e.g.*, radioactively labeled) monoclonal IgM antibodies used in the assays. The broadest method claim reads:

> 1. An immunoassay method utilizing an antibody to assay for a substance comprising hepatitis B-surface antigen (HBsAg) determinants which comprises the steps of:
> contacting a test sample containing said substance comprising HBsAg determinants with said antibody; and
> determining the presence of said substance in said

sample;
wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 109 M-1.

Certain claims were rejected under 35 U.S.C. § 103; these rejections have not ***735** been appealed. Remaining claims 1, 3, 7, 8, 14, 15, 19, and 25-27 were rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the disclosure would not enable a person skilled in the art to make and use the invention without undue experimentation. The rejection is directed solely to whether the specification enables one skilled in the art to make the monoclonal antibodies that are needed to practice the invention. The position of the PTO is that data presented by Wands show that the production of high-affinity IgM anti-HBsAg antibodies is unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies.

III. *Analysis*

A. *Enablement by Deposit of Microorganisms and Cell Lines.*

[1] The first paragraph of 35 U.S.C. § 112 requires that the specification of a patent must enable a person skilled in the art to make and use the claimed invention. "Patents * * * are written to enable those skilled in the art to practice the invention." [FN3] A patent need not disclose what is well known in the art. [FN4] Although we review underlying facts found by the board under a "clearly erroneous" standard, [FN5] we review enablement as a question of law. [FN6]

FN3. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed.Cir.1983), *cert. denied*, 469 U.S. 851, 105 S.Ct. 172, 83 L.Ed.2d 107 (1984).

FN4. *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed.Cir.1984).

FN5. *Coleman v. Dines*, 754 F.2d 353, 356, 224 USPQ 857, 859 (Fed.Cir.1985).

FN6. *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1268, 229 USPQ 805, 810 (Fed.Cir.1986), *cert. denied*, 479 U.S. 1030, 107 S.Ct. 875, 93 L.Ed.2d 829 (1987); *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 960 n. 6, 220 USPQ 592, 599 n. 6 (Fed.Cir.1983), *cert. denied*, 469 U.S. 835, 105 S.Ct. 127, 83 L.Ed.2d 69 (1984).

[2] Where an invention depends on the use of living materials such as microorganisms or cultured cells, it may be impossible to enable the public to make the invention (i.e., to obtain these living materials) solely by means of a written disclosure. One means that has been developed for complying with the enablement requirement is to deposit the living materials in cell depositories which will distribute samples to the public who wish to practice the invention after the patent issues. [FN7] Administrative guidelines and judicial decisions have clarified the conditions under which a deposit of organisms can satisfy the requirements of section 112. [FN8] A deposit has been held necessary for enablement where the starting materials (i.e., the living cells used to practice the invention, or cells from which the required cells can be produced) are not readily available to the public. [FN9] Even when starting materials are available, a deposit has been necessary where it would require undue experimentation to make the cells of the invention from the starting materials. [FN10]

FN7. *In re Argoudelis*, 434 F.2d 1390, 1392-93, 168 USPQ 99, 101-02 (CCPA 1970).

FN8. *In re Lundak*, 773 F.2d 1216, 227 USPQ 90 (Fed.Cir.1985); *Feldman v. Aunstrup*, 517 F.2d 1351, 186 USPQ 108 (CCPA 1975), *cert. denied*, 424 U.S. 912, 96 S.Ct. 1109, 47 L.Ed.2d 316 (1976); Manual of Patent Examining Procedure (MPEP) 608.01(p)(C) (5th ed. 1983, rev. 1987). *See generally* Hampar, *Patenting of Recombinant DNA Technology: The Deposit Requirement*, 67 J.Pat. Trademark Off. Soc'y 569 (1985).

FN9. *In re Jackson*, 217 USPQ 804, 807-08 (Bd.App.1982) (strains of a newly discovered species of bacteria isolated from nature); *Feldman*, 517 F.2d 1351, 186 USPQ 108 (uncommon fungus isolated from nature); *In re Argoudelis*, 434 F.2d at 1392, 168 USPQ at 102 (novel strain of antibiotic-producing microorganism isolated from nature); *In re Kropp*, 143 USPQ 148, 152 (Bd.App.1959) (newly discovered microorganism isolated from soil).

FN10. *In re Forman*, 230 USPQ 546, 547

(Bd.Pat.App. & Int.1986) (genetically engineered bacteria where the specification provided insufficient information about the amount of time and effort required); *In re Lundak*, 773 F.2d 1216, 227 USPQ 90 (unique cell line produced from another cell line by mutagenesis).

In addition to satisfying the enablement requirement, deposit of organisms also can be used to establish the filing date of the application as the prima facie date of invention,***736** [FN11] and to satisfy the requirement under 35 U.S.C. § 114 that the PTO be guaranteed access to the invention during pendency of the application. [FN12] Although a deposit may serve these purposes, we recognized, in *In re Lundak*, [FN13] that these purposes, nevertheless, may be met in ways other than by making a deposit.

FN11. *In re Lundak*, 773 F.2d at 1222, 227 USPQ at 95-96; *In re Feldman*, 517 F.2d at 1355, 186 USPQ at 113; *In re Argoudelis*, 434 F.2d at 1394-96, 168 USPQ at 103-04 (Baldwin, J. concurring).

FN12. *In re Lundak*, 773 F.2d at 1222, 227 USPQ at 95-96; *In re Feldman*, 517 F.2d at 1354, 186 USPQ at 112.

FN13. *In re Lundak*, 773 F.2d at 1222, 227 USPQ at 95-96.

A deposit also may satisfy the best mode requirement of section 112, first paragraph, and it is for this reason that the 1F8 hybridoma was deposited in connection with the '145 patent and the current application. Wands does not challenge the statements by the examiner to the effect that, although the deposited 1F8 line enables the public to perform immunoassays with antibodies produced by that single hybridoma, the deposit does not enable the generic claims that are on appeal. The examiner rejected the claims on the grounds that the written disclosure was not enabling and that the deposit was inadequate. Since we hold that the written disclosure fully enables the claimed invention, we need not reach the question of the adequacy of deposits.

B. *Undue Experimentation.*

[3][4][5] Although inventions involving microorganisms or other living cells often can be enabled by a deposit, [FN14] a deposit is not always necessary to satisfy the enablement requirement. [FN15] No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation. [FN16] Whether the specification in an application involving living cells (here, hybridomas) is enabled without a deposit must be decided on the facts of the particular case. [FN17]

FN14. *In re Argoudelis*, 434 F.2d at 1393, 168 USPQ at 102.

FN15. *Tabuchi v. Nubel*, 559 F.2d 1183, 194 USPQ 521 (CCPA 1977).

FN16. *Id.* at 1186-87, 194 USPQ at 525; *Merck & Co. v. Chase Chem. Co.*, 273 F.Supp. 68, 77, 155 USPQ 139, 146 (D.N.J.1967); *Guaranty Trust Co. v. Union Solvents Corp.*, 54 F.2d 400, 403-06, 12 USPQ 47, 50-53 (D.Del.1931), *aff'd*, 61 F.2d 1041, 15 USPQ 237 (3d Cir.1932), *cert. denied*, 288 U.S. 614, 53 S.Ct. 405, 77 L.Ed. 987 (1933); MPEP 608.01(p)(C) ("No problem exists when the microorganisms used are known and readily available to the public.").

FN17. *In re Jackson*, 217 USPQ at 807; *see In re Metcalfe*, 410 F.2d 1378, 1382, 161 USPQ 789, 792 (CCPA 1969).

[6] Appellants contend that their written specification fully enables the practice of their claimed invention because the monoclonal antibodies needed to perform the immunoassays can be made from readily available starting materials using methods that are well known in the monoclonal antibody art. Wands states that application of these methods to make high-affinity IgM anti-HBsAg antibodies requires only routine screening, and that does not amount to undue experimentation. There is no challenge to their contention that the starting materials (i.e., mice, HBsAg antigen, and myeloma cells) are available to the public. The PTO concedes that the methods used to prepare hybridomas and to screen them for high-affinity IgM antibodies against HBsAg were either well known in the monoclonal antibody art or adequately disclosed in the '145 patent and in the current application. This is consistent with this court's recognition with respect to another patent application that methods for obtaining and screening monoclonal antibodies were well known in 1980. [FN18] The sole issue is whether, in this particular case, it would require undue

experimentation to produce high-affinity IgM monoclonal antibodies.

FN18. *Hybritech,* 802 F.2d at 1384, 231 USPQ at 94.

[7] Enablement is not precluded by the necessity for some experimentation such as ***737** routine screening. [FN19] However, experimentation needed to practice the invention must not be undue experimentation. [FN20] "The key word is 'undue,' not 'experimentation.' " [FN21]

FN19. *Id.; Atlas Powder Co. v. E.I. DuPont De Nemours & Co.,* 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed.Cir.1984); *In re Angstadt,* 537 F.2d at 502-504, 190 USPQ at 218; *In re Geerdes,* 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974); *Mineral Separation, Ltd. v. Hyde,* 242 U.S. 261, 270-71, 37 S.Ct. 82, 86, 61 L.Ed. 286 (1916).

FN20. *Hybritech,* 802 F.2d at 1384, 231 USPQ at 94; *W.L. Gore,* 721 F.2d at 1557, 220 USPQ at 316; *In re Colianni,* 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977) (Miller, J., concurring).

FN21. *In re Angstadt,* 537 F.2d at 504, 190 USPQ at 219.

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* [448 F.2d 872, 878-79; 169 USPQ 759, 762-63 (2d Cir.1971), *cert. denied,* 404 U.S. 1018, 92 S.Ct. 680, 30 L.Ed.2d 666 (1972)]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed * * *. [FN22]

FN22. *In re Jackson,* 217 USPQ at 807.

[8] The term "undue experimentation" does not appear in the statute, but it is well established that enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. [FN23] Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. The board concluded that undue experimentation would be needed to practice the invention on the basis of experimental data presented by Wands. These data are not in dispute. However, Wands and the board disagree strongly on the conclusion that should be drawn from that data.

FN23. *See Hybritech,* 802 F.2d at 1384, 231 USPQ at 94; *Atlas Powder,* 750 F.2d at 1576, 224 USPQ at 413.

[9] Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *In re Forman.* [FN24] They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. [FN25]

FN24. *In re Forman,* 230 USPQ at 547.

FN25. *Id.; see In re Colianni,* 561 F.2d at 224, 195 USPQ at 153 (Miller, J., concurring); *In re Rainer,* 347 F.2d 574, 577, 146 USPQ 218, 221 (CCPA 1965).

In order to understand whether the rejection was proper, it is necessary to discuss further the methods for making specific monoclonal antibodies. The first step for making monoclonal antibodies is to immunize an animal. The '145 patent provides a detailed description of procedures for immunizing a specific strain of mice against HBsAg. Next the spleen, an organ rich in lymphocytes, is removed and the lymphocytes are separated from the other spleen cells. The lymphocytes are mixed with myeloma cells, and the mixture is treated to cause a few of the cells to fuse with each other. Hybridoma cells that secrete the desired antibodies then must be isolated from the enormous number of other cells in the mixture. This is done through a series of screening procedures.

The first step is to separate the hybridoma cells from unfused lymphocytes and myeloma cells. The cells are cultured in a medium in which all the lymphocytes and myeloma cells die, and only the hybridoma cells survive. The next step is to isolate and clone hybridomas that make antibodies ***738** that bind to the antigen of interest. Single hybridoma

cells are placed in separate chambers and are allowed to grow and divide. After there are enough cells in the clone to produce sufficient quantities of antibody to analyze, the antibody is assayed to determine whether it binds to the antigen. Generally, antibodies from many clones do not bind the antigen, and these clones are discarded. However, by screening enough clones (often hundreds at a time), hybridomas may be found that secrete antibodies against the antigen of interest.

Wands used a commercially available radioimmunoassay kit to screen clones for cells that produce antibodies directed against HBsAg. In this assay the amount of radioactivity bound gives some indication of the strength of the antibody-antigen binding, but does not yield a numerical affinity constant, which must be measured using the more laborious Scatchard analysis. In order to determine which anti-HBsAg antibodies satisfy all of the limitations of appellants' claims, the antibodies require further screening to select those which have an IgM isotype and have a binding affinity constant of at least 109 M-1. [FN26] The PTO does not question that the screening techniques used by Wands were well known in the monoclonal antibody art.

> FN26. The examiner, the board, and Wands all point out that, technically, the strength of antibody-HBsAg binding is measured as *avidity,* which takes into account multiple determinants on the HBsAg molecule, rather than affinity. Nevertheless, despite this correction, all parties then continued to use the term "affinity." We will use the terminology of the parties. Following the usage of the parties, we will also use the term "high-affinity" as essentially synonymous with "having a binding affinity constant of at least 109 M-1.

During prosecution Wands submitted a declaration under 37 C.F.R. § 1.132 providing information about all of the hybridomas that appellants had produced before filing the patent application. The first four fusions were unsuccessful and produced no hybridomas. The next six fusion experiments all produced hybridomas that made antibodies specific for HBsAg. Antibodies that bound at least 10,000 cpm in the commercial radioimmunoassay were classified as "high binders." Using this criterion, 143 high-binding hybridomas were obtained. In the declaration, Wands stated that [FN27]

> FN27. A table in the declaration presented the binding data for antibodies from every cell line. Values ranged from 13,867 to 125,204 cpm, and a substantial proportion of the antibodies showed binding greater than 50,000 cpm. In confirmation of Dr. Wand's statement, two antibodies with binding less than 25,000 cpm were found to have affinity constants greater than 109 M-1.
>
> It is generally accepted in the art that, among those antibodies which are binders with 50,000 cpm or higher, there is a very high likelihood that high affinity (Ka [greater than] 109 M-1-1) antibodies will be found. However, high affinity antibodies can also be found among high binders of between 10,000 and 50,000, as is clearly demonstrated in the Table.
> The PTO has not challenged this statement.

The declaration stated that a few of the high-binding monoclonal antibodies from two fusions were chosen for further screening. The remainder of the antibodies and the hybridomas that produced them were saved by freezing. Only nine antibodies were subjected to further analysis. Four (three from one fusion and one from another fusion) fell within the claims, that is, were IgM antibodies and had a binding affinity constant of at least 109 M-1-1. Of the remaining five antibodies, three were found to be IgG, while the other two were IgM for which the affinity constants were not measured (although both showed binding well above 50,000 cpm).

Apparently none of the frozen cell lines received any further analysis. The declaration explains that after useful high-affinity IgM monoclonal antibodies to HBsAg had been found, it was considered unnecessary to return to the stored antibodies to screen for more IgMs. Wands says that the existence of the stored hybridomas was disclosed to the PTO to comply with the requirement under 37 C.F.R. § 1.56 that applicants fully disclose all of their relevant ***739** data, and not just favorable results. [FN28] How these stored hybridomas are viewed is central to the positions of the parties.

> FN28. *See Rohm & Haas Co. v. Crystal Chem. Co.,* 722 F.2d 1556, 220 USPQ 289 (Fed.Cir.1983).

The position of the board emphasizes the fact that since the stored cell lines were not completely tested, there is no proof that any of them are IgM antibodies with a binding affinity constant of at least 109 M-1-1. Thus, only 4 out of 143 hybridomas, or 2.8 percent,

were *proved* to fall within the claims. Furthermore, antibodies that were proved to be high-affinity IgM came from only 2 of 10 fusion experiments. These statistics are viewed by the board as evidence that appellants' methods were not predictable or reproducible. The board concludes that Wands' low rate of demonstrated success shows that a person skilled in the art would have to engage in undue experimentation in order to make antibodies that fall within the claims.

Wands views the data quite differently. Only nine hybridomas were actually analyzed beyond the initial screening for HBsAg binding. Of these, four produced antibodies that fell within the claims, a respectable 44 percent rate of success. (Furthermore, since the two additional IgM antibodies for which the affinity constants were never measured showed binding in excess of 50,000 cpm, it is likely that these also fall within the claims.) Wands argues that the remaining 134 unanalyzed, stored cell lines should not be written off as failures. Instead, if anything, they represent partial success. Each of the stored hybridomas had been shown to produce a high-binding antibody specific for HBsAg. Many of these antibodies showed binding above 50,000 cpm and are thus highly likely to have a binding affinity constant of at least 109 M-1-1. Extrapolating from the nine hybridomas that were screened for isotype (and from what is well known in the monoclonal antibody art about isotype frequency), it is reasonable to assume that the stored cells include some that produce IgM. Thus, if the 134 incompletely analyzed cell lines are considered at all, they provide some support (albeit without rigorous proof) to the view that hybridomas falling within the claims are not so rare that undue experimentation would be needed to make them.

The first four fusion attempts were failures, while high-binding antibodies were produced in the next six fusions. Appellants contend that the initial failures occurred because they had not yet learned to fuse cells successfully. Once they became skilled in the art, they invariably obtained numerous hybridomas that made high-binding antibodies against HBsAg and, in each fusion where they determined isotype and binding affinity they obtained hybridomas that fell within the claims.

Wands also submitted a second declaration under 37 C.F.R. § 1.132 stating that after the patent application was submitted they performed an eleventh fusion experiment and obtained another hybridoma that made a high-affinity IgM anti-HBsAg antibody. No information was provided about the number of clones screened in that experiment. The board determined that, because there was no indication as to the number of hybridomas screened, this declaration had very little value. While we agree that it would have been preferable if Wands had included this information, the declaration does show that when appellants repeated their procedures they again obtained a hybridoma that produced an antibody that fit all of the limitations of their claims.

We conclude that the board's interpretation of the data is erroneous. It is strained and unduly harsh to classify the stored cell lines (each of which was proved to make high-binding antibodies against HBsAg) as failures demonstrating that Wands' methods are unpredictable or unreliable. [FN29] At worst, they prove nothing at all about the probability of success, and merely show ***740** that appellants were prudent in not discarding cells that might someday prove useful. At best, they show that high-binding antibodies, the starting materials for IgM screening and Scatchard analysis, can be produced in large numbers. The PTO's position leads to the absurd conclusion that the more hybridomas an applicant makes and saves without testing, the less predictable the applicant's results become. Furthermore, Wands' explanation that the first four attempts at cell fusion failed only because they had not yet learned to perform fusions properly is reasonable in view of the fact that the next six fusions were all successful. The record indicates that cell fusion is a technique that is well known to those of ordinary skill in the monoclonal antibody art, and there has been no claim that the fusion step should be more difficult or unreliable where the antigen is HBsAg than it would be for other antigens.

> FN29. Even if we were to accept the PTO's 2.8% success rate, we would not be required to reach a conclusion of undue experimentation. Such a determination must be made in view of the circumstances of each case and cannot be made solely by reference to a particular numerical cutoff.

When Wands' data is interpreted in a reasonable manner, analysis considering the factors enumerated in *In re Forman* leads to the conclusion that undue experimentation would not be required to practice the invention. Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.

The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen. However, it seems unlikely that undue experimentation would be defined in terms of the number of hybridomas that were never screened. Furthermore, in the monoclonal antibody art it appears that an "experiment" is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen. This process entails immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics. Wands carried out this entire procedure three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations. Reasonably interpreted, Wands' record indicates that, in the production of high-affinity IgM antibodies against HBsAG, the amount of effort needed to obtain such antibodies is not excessive. Wands' evidence thus effectively rebuts the examiner's challenge to the enablement of their disclosure. [FN30]

FN30. *In re Strahilevitz*, 668 F.2d 1229, 1232, 212 USPQ 561, 563 (CCPA 1982).

IV. *Conclusion*

Considering all of the factors, we conclude that it would not require undue experimentation to obtain antibodies needed to practice the claimed invention. Accordingly, the rejection of Wands' claims for lack of enablement under 35 U.S.C. § 112, first paragraph, is reversed.

REVERSED

PAULINE NEWMAN, Circuit Judge, concurring in part, dissenting in part.

A

I concur in the court's holding that additional samples of hybridoma cell lines that produce these high-affinity IgM monoclonal antibodies need not be deposited. This invention, as described by Wands, is not a selection of a few rare cells from many possible cells. To the contrary, Wands states that all monoclonally produced IgM antibodies to hepatitis B surface antigen have the desired high avidity and other favorable properties, and that all are readily preparable by now-standard techniques.

Wands states that his United States Patent No. 4,271,145 describes fully operable techniques, and is distinguished from his ***741** first four failed experiments that are referred to in the Rule 132 affidavit. Wands argues that these biotechnological mechanisms are relatively well understood and that the preparations can be routinely duplicated by those of skill in this art, as in *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380, 231 USPQ 81, 94 (Fed.Cir.1986), *cert. denied*, 480 U.S. 947, 107 S.Ct. 1606, 94 L.Ed.2d 792 (1987). I agree that it is not necessary that there be a deposit of multiple exemplars of a cell system that is readily reproduced by known, specifically identified techniques.

B

I would affirm the board's holding that Wands has not complied with 35 U.S.C. § 112, first paragraph, in that he has not provided data sufficient to support the breadth of his generic claims. Wands' claims on appeal include the following:

> 19. Monoclonal high affinity IgM antibodies immunoreactive with HBsAg determinants, wherein said antibodies are coupled to an insoluble solid phase, and wherein the binding affinity constant of said antibodies for said HBsAg determinants is at least 109 M-1-1.
>
> 26. Monoclonal high affinity IgM antibodies immunoreactive with HBsAg determinants wherein said antibodies are detectably labelled.

Wands states that he obtained 143 "high binding monoclonal antibodies of the right specificity" in the successful fusions; although he does not state how they were determined to be high binding or of the right specificity, for Wands also states that only nine of these 143 were tested.

Of these nine, four (three from one fusion and one from another fusion) were found to have the claimed high affinity and to be of the IgM isotype. Wands states that the other five were either of a different isotype or their affinities were not determined. (This latter statement also appears to contradict his statement that all 143 were "high binding".)

Wands argues that a "success rate of four out of nine", or 44.4%, is sufficient to support claims to the entire class. The Commissioner deems the success rate to be four out of 143, or 2.8%; to which Wands

responds with statistical analysis as to how unlikely it is that Wands selected the only four out of 143 that worked. Wands did not, however, prove the right point. The question is whether Wands, by testing nine out of 143 (the Commissioner points out that the randomness of the sample was not established), and finding that four out of the nine had the desired properties, has provided sufficient experimental support for the breadth of the requested claims, in the context that "experiments in genetic engineering produce, at best, unpredictable results", quoting from *Ex parte Forman*, 230 USPQ 546, 547 (Bd.Pat.App. and Int.1986).

The premise of the patent system is that an inventor, having taught the world something it didn't know, is encouraged to make the product available for public and commercial benefit, by governmental grant of the right to exclude others from practice of that which the inventor has disclosed. The boundary defining the excludable subject matter must be carefully set: it must protect the inventor, so that commercial development is encouraged; but the claims must be commensurate with the inventor's contribution. Thus the specification and claims must meet the requirements of 35 U.S.C. § 112. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 23-24 (CCPA 1970).

As the science of biotechnology matures the need for special accommodation, such as the deposit of cell lines or microorganisms, may diminish; but there remains the body of law and practice on the need for sufficient disclosure, including experimental data when appropriate, that reasonably support the scope of the requested claims. That law relates to the sufficiency of the description of the claimed invention, and if not satisfied by deposit, must independently meet the requirements of Section 112.

Wands is not claiming a particular, specified IgM antibody. He is claiming all such monoclonal antibodies in assay for hepatitis B surface antigen, based on his teaching that such antibodies have uniformly reproducible high avidity, free of the known ***742** disadvantages of IgM antibodies such as tendency to precipitate or aggregate. It is incumbent upon Wands to provide reasonable support for the proposed breadth of his claims. I agree with the Commissioner that four exemplars shown to have the desired properties, out of the 143, do not provide adequate support.

Wands argues that the law should not be "harsher" where routine experiments take a long time. However, what Wands is requesting is that the law be less harsh. As illustrated in extensive precedent on the question of how much experimentation is "undue", each case must be determined on its own facts. *See, e.g., W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed.Cir.1983), *cert. denied*, 469 U.S. 851, 105 S.Ct. 172, 83 L.Ed.2d 107 (1984); *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 218 (CCPA 1976); *In re Cook*, 439 F.2d 730, 734-35, 169 USPQ 298, 302-03 (CCPA 1971).

The various criteria to be considered in determining whether undue experimentation is required are discussed in, for example, *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1971); *In re Rainer*, 347 F.2d 574, 146 USPQ 218 (CCPA 1965); *Ex parte Forman*, 230 USPQ at 547. Wands must provide sufficient data or authority to show that his results are reasonably predictable within the scope of the claimed generic invention, based on experiment and/or scientific theory. In my view he has not met this burden.

Briefs and Other Related Documents **(Back to top)**

- 1987 WL 882253 (Appellate Brief) Reply Brief for Appellants (Nov. 13, 1987)Original Image of this Document (PDF)

- 1987 WL 882252 (Appellate Brief) Brief for the Commissioner of Patents and Trademarks (Oct. 27, 1987)Original Image of this Document (PDF)

- 1987 WL 882251 (Appellate Brief) Brief for Appellants (Sep. 14, 1987)Original Image of this Document (PDF)

END OF DOCUMENT

United States Court of Customs and Patent Appeals.
Norman A. NELSON, Appellant,
v.
Jean BOWLER et al., Appellees.
Appeal No. 79-630.

July 31, 1980.
Rehearing Denied Nov. 6, 1980.

In a patent interference proceeding, Interference No. 98,926, the Board of Patent Interferences awarded priority and appeal was taken. The Court of Customs and Patent Appeals, Rich, J., held that tests showing smooth muscle stimulation and blood pressure modulation established practical utility of 16-phenoxy-substituted prostaglandins.

Reversed.

West Headnotes

[1] **Patents** 49
291k49 Most Cited Cases
Where counts of application did not recite any particular utility for drug, evidence of any utility was sufficient.

[2] **Patents** 49
291k49 Most Cited Cases
Tests evidencing pharmacological activity may manifest a practical utility for drug even though they may not establish a specific therapeutic use.

[3] **Patents** 49
291k49 Most Cited Cases
Adequate proof of pharmacological activity of drug constitutes a showing of practical utility.

[4] **Patents** 47
291k47 Most Cited Cases
Where test for pharmacological activity is reasonably indicative of desired response, rigorous correlation is not necessary.

[5] **Patents** 48
291k48 Most Cited Cases
Tests showing smooth muscle stimulation and blood pressure modulation established practical utility of 16-phenoxy-substituted prostaglandins.

[6] **Patents** 97
291k97 Most Cited Cases
Speculative inaccuracies in application's alleged utilities for drug amounted at most to simple negligence and did not constitute fraud.

[7] **Patents** 91(4)
291k91(4) Most Cited Cases
Evidence in interference proceeding involving 16-phenoxy-substituted prostaglandins established applicant's prior actual reduction to practice.

***854** Robert A. Armitage, Kalamazoo, Mich., and Thomas J. Macpeak, Washington, D. C., for appellant; Peter D. Olexy, Washington, D. C., of counsel.

Paul N. Kokulis, Washington, D. C., for appellees; William T. Bullinger and J. D. Atkinson, of counsel.

Before MARKEY, Chief Judge, RICH, BALDWIN, and MILLER, Judges, and RE, Judge. [FN*]

FN* The Honorable Edward D. Re, Chief Judge, United States Customs Court, sitting by designation.

RICH, Judge.

This appeal is from the decision of the United States Patent and Trademark Office (PTO) Board of Patent Interferences (board) awarding priority on all four counts to Bowler et al. (Bowler), the senior party. We reverse.

This interference involves two applications, serial No. 252,030, filed by appellant Nelson May 10, 1972, for "Composition and Process" and serial No. 474,608, filed by Bowler May 30, 1974, as a continuation of serial No. 248,717 filed April 28, 1972, for "Cyclopentane Derivatives." Appellee was accorded the benefit of an application filed in Great Britain on May 11, 1971, under 35 U.S.C. s 119, and was designated senior party. Only Nelson took testimony.

The real parties in interest are Upjohn Company, assignee of Nelson, and Imperial Chemical Industries, Limited, assignee of Bowler.

The Subject Matter

Three counts remain in this appeal.[FN1] Counts 2 and 4 describe 16- phenoxy-substituted

prostaglandins (PG's) which are admitted to be structurally related to known, naturally-occurring prostaglandins commonly designated PGF 2 and PGE 2.[FN2] ***855** Count 1 is directed toward intermediates used to prepare the 16-phenoxy PG compounds of counts 2 and 4.

> FN1. Count 3 employed compounds within count 2 in a method of inducing luteolysis (abortion caused by separation of the corpus luteum from the uterine wall). This count was expressly abandoned by Nelson at oral argument and in his brief.
>
> FN2. "Natural prostaglandins" refers to PG's which have structures corresponding to those which occur in nature. While the art can synthesize natural PG's, the "natural" designation is retained to identify structure rather than origin.

Naturally occurring PG's allegedly had recognized value in pharmacology at the time the present invention was made. Both parties stated as much in their respective specifications. Effects such as smooth muscle stimulation and blood pressure modulation were said to be reflected in various commercial applications. For example, labor induction or abortion was attributed to uterine smooth muscle stimulation caused by administration of PG's. Modification of blood pressure, on the other hand, was purportedly useful in treating either shock or hypertension since natural PG's can either raise or lower blood pressure.

The Issue

The issue is whether Nelson has shown at least one utility for counts 1, 2, and 4 which sufficiently establishes an actual reduction to practice before the critical date of May 11, 1971. Specifically, is a practical utility manifested in testing 16-phenoxy PG's for their stimulation of smooth muscle tissue from gerbil colons and their modulation of blood pressure in rats?

The Evidence

Two tests conducted at Upjohn before the critical date are relied upon by appellant to prove practical utility. They are referred to as the rat blood pressure (BP) test and the gerbil colon smooth muscle stimulation (GC-SMS) test. The comparison standards for both were selected from naturally occurring PG's, i. e., PGE sub1 and PGF sub2 , having known blood pressure and smooth muscle stimulation responses.

In the BP test, the blood pressure of anesthetized rats recorded on a polygraph chart to determine whether an injected compound had any effect. Responses were categorized as either a depressor (lowering) effect or a pressor (elevating) effect. Calibration was supposedly achieved by comparing an unknown analog PG versus either a standard natural PG depressor, such as PGF sub2 , or a standard natural PG pressor, such as PGE sub1 . Each rat was given successive PG's to test. Allowance was made for the blood pressure to approach a normal level before administering another PG.

The tested compounds, labeled 38980 and 38669, were both reported to give an atypical or biphasic response. That is, both initially depressed the rat's blood pressure before raising it. The depressor effect was a temporary manifestation lasting several seconds. The subsequent pressor effect, however, was a strong response lasting several hours. Nelson exhibits 27 and 28, the test results for the above-mentioned compounds, reflect an equivalent activity between the above analog compounds and the naturally occurring compounds.

During the testimony period of this interference, Dr. James Weeks, another Upjohn research scientist, was questioned about the reliability of the BP test. He answered that, as of April 1971, this test had been in use for between five and six years. In that period, he said it gave excellent results.

The GC-SMS test was in vitro as opposed to the in vivo BP test. Purportedly, Upjohn technicians excised a section of colon from a freshly-killed gerbil for suspension in a physiological solution. A lever arm was connected to the colon in such a way that any contraction was recorded as a polygraph trace. For comparison purposes, PGE, a known smooth muscle stimulant, was employed. Both of Nelson's tested analog compounds were said to closely approximate the response of the natural compounds.

Board Decision

Both conception and preparation by Nelson of compounds within the scope of counts 1, 2, and 4 were held to have occurred prior to the critical date. Since the counts did not recite any utility, the board declared that the 16-phenoxy PG's, could have any practical utility, i. e., utility sufficient for an actual reduction to practice, citing Blicke v. Treves, 44 CCPA 753, 241 F.2d 718, 112 USPQ 472 (1957). But priority was not awarded to Nelson because his ***856** evidence was held not to show adequate proof of

practical utility.

The tests used by Nelson were characterized as "rough screens, uncorrelated with actual utility." The board said neither the biphasic pressor effect in rats nor the stimulation of gerbil colon smooth muscle revealed a practical utility, citing Rey-Bellet v. Engelhardt, 493 F.2d 1380, 181 USPQ 453 (Cust. & Pat.App.1974). The present situation was compared to that in Knapp v. Anderson, 477 F.2d 588, 177 USPQ 688 (Cust. & Pat.App.1973), where only a potential utility was established.

Finally, Nelson's conduct, as evidenced by statements in his application, was evaluated for inequitable conduct which might establish fraud. The clear and convincing proof necessary to establish fraud was held to be missing. The board stated that Bowler failed to show how Nelson had either misled the examiner or knowingly presented false information. Speculative statements of utility were found insufficient to establish inequitable conduct.

OPINION

Practical Utility

[1][2] The board correctly stated that evidence of any utility is sufficient since the counts do not recite any particular utility. Blicke v. Treves, supra. However, we cannot agree with its conclusion that the pharmacological activity evidenced by the BP and the GC-SMS tests does not establish a practical utility. Even though Nelson now admits that antifertility activity such as luteolysis is not proven by these tests, the board erred in not recognizing that tests evidencing pharmacological activity may manifest a practical utility even though they may not establish a specific therapeutic use.

"Practical utility" is a shorthand way of attributing "real-world" value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public.

[3] Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility.

[4] Bowler argues that the BP and GC-SMS tests are inconclusive showings of pharmacological activity since confirmation by statistically significant means, i. e., a 4-point assay,[FN4] occurred after the critical date. But a rigorous correlation is not necessary where the test for pharmacological activity is reasonably indicative of the desired response. While Dr. Brown, an Upjohn PG researcher, testified that treatment of one muscle with various successive compounds, as done here, could involve a small residual carryover effect from one compound to another, he also indicated that the correlation between the "preliminary" test and 4-point assays was reasonably certain. In view of the above correlation, the 4-point assay, while preferable, was not the sole means for establishing practical utility.

> FN4. A 4-point assay consists of testing one compound against one standard in either four rats or on four gerbil colons.

We also do not attach much significance to the atypical blood pressure response in the BP test. The record states that the biphasic nature was predominantly a sustained pressor effect, a known activity of certain natural PG's [FN5] with established therapeutic uses. Nor are we concerned with the admitted variability of smooth muscle responses. Even with known PG's the response differs among smooth muscles. The controlling point is that these responses are evidence of pharmacological activity. As this court said in Blicke, supra,

> FN5. In fact, Charles Lawson, an Upjohn research associate, stated that sometimes even PGF 2 manifested a biphasic effect.

> ***857** * * * whether a composition of matter must be tested in order to establish a reduction to practice, and if so, what tests are necessary, is a question which must be decided on the basis of the facts of the particular case involved.

This appeal is not analogous, as the board suggests, to Rey-Bellet v. Engelhardt, supra, even though the issues are similar. There, a new drug, nortriptyline (NTL), and one of its known analogs, amitriptyline (N-methyl substituted NTL), were tested. The results were subsequently offered to prove practical utility for NTL. For example, the "General Mental Health Screening Test" was designed to check for "physical responses." The presence or absence of a response in a test animal after an injection could have indicated pharmacological activity.

The inherent lack of certainty in this test resulted in a failure to prove practical utility. While Engelhardt advocated that pupil dilation evidenced anticholinergic activity,[FN6] this court did not find adequate correlation between them. The Mental Health test was found not to be specific for the claimed activity since drugs without that activity could have caused pupil dilation.

> FN6. Anticholinergic action describes the blocking of neural impulses passing along the parasympathetic or autonomic nervous system which includes ocular nerves.

We specifically note that anticholinergic activity was the sole utility maintained by Engelhardt for the purposes of the Mental Health test. He did not argue that pupil dilation in itself was a useful pharmacological activity. Without such an argument, proof of pupil responses, alone, did not establish an actual reduction to practice.

Engelhardt also argued that since amitryptyline, a compound of proven utility, had a very close structural similarity to NTL and produced similar test results, the utility of NTL had been proved. However, the Mental Health test was found to be unsuitable for detecting any of the known useful pharmacological activities possessed by the analog. Thus Engelhardt's argument of utility based upon analog similarity was equally invalid because of inconclusive proof.

Another test in Rey-Bellet, the "tetrabenazine antagonism" test, supposedly evidenced antidepressant activity. Mice tranquilized by tetrabenazine were said to simulate depressed humans and animals. Antagonizing or offsetting the tranquilizer was interpreted as a sign of activity.[FN7] This court concluded that insufficient experience with the test precluded a showing of "the necessary correlation between tetrabenazine antagonism in mice and antidepressant activity in man (or animals)." Rey-Bellet, 493 F.2d at 1384, 181 USPQ at 456.

> FN7. Again, we note that tranquilizer antagonism alone was not argued to be a practical utility.

[5] We find Rey-Bellet to be distinguishable on its facts. According to the present evidence, specific pharmacological activities, i. e., smooth muscle stimulation and blood pressure modulation, were recognized as practical utilities. These activities were directly measured by dispositive tests. In other words, one skilled in the art at the time the tests were performed would have been reasonably certain that 16-phenoxy PG's had practical utility.

Bowler urges that Knapp v. Anderson, supra, supports their contention that the instant tests were evidence only of potential utility. We disagree. The laboratory testing in Knapp was conducted outside the "intended functional setting" and was not related to pharmacological activity. A claimed amine was allegedly useful as an ashless dispersant in lubricants for internal combustion engines. This court found that one skilled in the art would not find a practical utility solely in the results of a bench test for sludge dispersancy. Nor could one reasonably predict a practical utility therefrom since the losing party failed to establish a correlation between performance in the bench test and that within an engine.

Here, however, a correlation between test results and pharmacological activities has ***858** been established. The BP test inherently was of such a nature since it is performed in vivo and directly evidences the claimed activity. While the GC-SMS test is in vitro, both parties admit that it adequately simulates in vivo colon smooth muscle stimulation.

Fraud

[6] Bowler must demonstrate that Nelson committed fraud by clear and convincing evidence. Norton v. Curtiss, 57 CCPA 1384, 1408, 433 F.2d 779, 797, 167 USPQ 532, 546-47 (1970). We agree with the board that he has not carried this heavy burden.

While Bowler accurately states that an applicant must recite utility with as reasonable a certainty as possible, i. e., without total disregard of facts within his knowledge, the speculative inaccuracies in Nelson's alleged utilities amount at most to simple negligence. While we do not sanction the use of boilerplate utility disclosures without regard to known contrary facts, this alone is insufficient to support a charge of fraud. Nowhere does Bowler show a clear intent by Nelson to mislead the examiner by false utility statements.

Summary

[7] In the final analysis, every utility question arising in an interference must be decided on its own facts. Relevant evidence is judged as a whole for its persuasiveness in linking observed properties to suggested uses. Reasonable correlation between the two is sufficient for an actual reduction to practice. For the above reasons, we hold that Nelson sustained

his burden of proving a prior actual reduction to practice.

The decision of the board awarding priority on counts 1, 2, and 4 to Bowler is reversed.

REVERSED.

626 F.2d 853, 206 U.S.P.Q. 881

END OF DOCUMENT

▷

Briefs and Other Related Documents

United States Court of Appeals,
Federal Circuit.
Donald G. RICHARDSON, Plaintiff/Appellant,
v.
SUZUKI MOTOR CO., LTD. and U.S. Suzuki Motor Corporation, Defendants/Cross-Appellants,
Kawasaki Heavy Indust. Ltd., Kawasaki Motors Corp., Yamaha Motor Co., Ltd., Yamaha Motor Corp., U.S.A., Kayaba Industry Co., Ltd. and Kayaba Industry Co.,
Defendants.
Nos. 87-1497, 87-1498, 87-1502, 88-1083 and 88-1084.

Feb. 16, 1989.
Rehearing Denied March 29, 1989.
Suggestion for Rehearing In Banc Declined May 4, 1989.

Appeals were taken from order of the United States District Court for the Central District of California, William P. Gray, J., entered following jury verdict in action for patent infringement, breach of contract, fraud, and misappropriation of trade secrets. The Court of Appeals, Pauline Newman, Circuit Judge, held that: (1) evidence sustained finding of validity; (2) evidence sustained finding of infringement; (3) evidence sustained finding of fraud; (4) evidence sustained finding of misappropriation of trade secrets; but (5) court's instruction on damages was improper.

Affirmed in part, reversed in part, vacated in part, and remanded.

West Headnotes

[1] Patents 314(5)
291k314(5) Most Cited Cases
Jury may decide the questions of anticipation and obviousness, either as separate special verdicts or en route to a verdict on the question of validity, which may also be decided by the jury. 35 U.S.C.A. § § 102, 103.

[2] Federal Courts 846
170Bk846 Most Cited Cases

[2] Federal Courts 847
170Bk847 Most Cited Cases
When judgment arises from jury verdict, reviewing court applies the reasonable jury and substantial evidence standard, a standard which gives greater deference to the judgment simply because appellate review is more limited, compared with review of the trial judge's decision.

[3] Patents 72(1)
291k72(1) Most Cited Cases
Invention is anticipated if the same device, including all the claim limitations, is shown in a single prior art reference; every element of the claimed invention must be literally present, arranged as in the claim. 35 U.S.C.A. § 102.

[4] Patents 72(1)
291k72(1) Most Cited Cases
In order for there to be anticipation, the identical invention must be shown in as complete detail as is contained in the patent claim. 35 U.S.C.A. § 102.

[5] Patents 72(1)
291k72(1) Most Cited Cases
It was error to instruct the jury that anticipation can be shown by equivalents, a legal theory that is pertinent to obviousness, not to anticipation. 35 U.S.C.A. § § 102, 103.

[6] Patents 312(6)
291k312(6) Most Cited Cases
Evidence sustained finding that patent covering rear wheel suspension system for motorcycle to smooth the ride over rough terrain was not invalid for anticipation. 35 U.S.C.A. § 102.

[7] Patents 324.55(3.1)
291k324.55(3.1) Most Cited Cases
(Formerly 291k324.55(3))
Review of jury determination as to whether challenger has proven invalidity by clear and convincing evidence is whether reasonable jurors could have concluded that the challenger failed to meet the burden.

[8] Patents 36(3)
291k36(3) Most Cited Cases
Evidence sustained jury finding that patent on rear

wheel suspension for motorcycles intended for off-road use was not invalid for obviousness. 35 U.S.C.A. § 103.

[9] Patents 324.56
291k324.56 Most Cited Cases
Although district court erred in its belief that obviousness could only be presented to the jury for an advisory verdict, reviewing court could view the trial court's agreement with the jury verdict of validity as supporting the court's denial of posttrial motions for judgment n.o.v. and for new trial on the issue of obviousness.

[10] Patents 312(6)
291k312(6) Most Cited Cases
Patent holder bore the burden of proving infringement by preponderance of the evidence.

[11] Patents 314(5)
291k314(5) Most Cited Cases
Jury was the finder of fact of infringement.

[12] Patents 314(6)
291k314(6) Most Cited Cases
Jury special verdict as to whether defendant's motorcycle rear wheel suspension infringed the plaintiff's patent which stated "yes, with the rising rate" was not a limitation of the finding of infringement to the rising rate claim but, rather, was a response to the defendant's argument that the two suspensions were not the same because of a different rising rate.

[13] Patents 324.56
291k324.56 Most Cited Cases
It was highly prejudicial to instruct the jury on the differences between linkages involved in patented device and allegedly infringing device while remaining silent on the similarities and to give the dictionary definition of equivalent as meaning "corresponding or virtually identical, especially in effect or function.".

[14] Patents 324.56
291k324.56 Most Cited Cases
It was prejudicial to give special verdicts in patent case which isolated specific claim elements so that it was removed from the perspective that is obtained only when the claimed invention is viewed in its entirety.

[15] Patents 240
291k240 Most Cited Cases
Device which embodies improvements on a claimed structure does not automatically avoid the reach of the claim.

[16] Patents 312(5)
291k312(5) Most Cited Cases
Evidence sustained finding that patent on rear wheel suspension for motorcycles intended for off-road riding was infringed.

[17] Patents 324.55(1)
291k324.55(1) Most Cited Cases
Court reviews award of damages for patent infringement on the reasonable jury/substantial evidence standard.

[18] Patents 324.56
291k324.56 Most Cited Cases
Court's error in instructing jury that it had found a minor infringement required reversal of award of damages.

[19] Contracts 353(8)
95k353(8) Most Cited Cases
It was error to instruct jury in breach of contract action in a manner which limited the scope of information which the defendant had agreed to protect more narrowly than that set forth in the contract and to instruct the jury accordingly as to the defendant's obligations under the contract.

[20] Trade Regulation 1001
382k1001 Most Cited Cases
(Formerly 379k27)
Burden of proof was on plaintiff to prove that his information met legal requirements of protectible trade secret.

[21] Trade Regulation 1002
382k1002 Most Cited Cases
(Formerly 379k27)
Evidence that contract between inventor and manufacturer stated that manufacturer agreed not to use or disclose technical information, know how, inventions, use data, and design specifications which it received from the inventor demonstrated that the information provided to the manufacturer was protectible trade secrets.

[22] Trade Regulation 984
382k984 Most Cited Cases
(Formerly 379k10(5))
Under California law, manufacturer which received trade secrets from inventor was not entitled to use as

its own any information which it could have independently discovered and fact that it could have accomplished on its own whatever the inventor contributed to it did not eliminate its liability for misappropriation of trade secrets.

[23] Trade Regulation 984
382k984 Most Cited Cases
(Formerly 379k10(5))
Under California law, slavish copying is not necessary for misappropriation of a trade secret and independent judgment does not remove the information from protection.

[24] Patents 1
291k1 Most Cited Cases

[24] Trade Regulation 984
382k984 Most Cited Cases
(Formerly 379k10(5))
Legal status of information and improvements made to an invention after patent application has been filed is independent of the presence, or absence, of the patent application or ensuing patent; information and improvements may be separately patentable, they may be preserved in confidence and disclosed only in accordance with the agreement, and they are protected against
misappropriation in accordance with the laws of the contract and tort.

[25] Copyrights and Intellectual Property 104
99k104 Most Cited Cases
Information which manufacturer sought from inventor and as to which it agreed to respect confidentiality was intellectual property in the eyes of the law and protected in accordance with the law.

[26] Trade Regulation 990
382k990 Most Cited Cases
(Formerly 379k10(5))
Inventor's design modifications to rear wheel suspension for off-road motorcycle which would extend the rear wheel travel over earlier rising-rate designs and design of an alternate mount were trade secrets.

[27] Labor and Employment 309
231Hk309 Most Cited Cases
(Formerly 291k93)
Commercial arrangement wherein inventor agreed to facilitate manufacturer's testing and evaluation of the inventor's invention did not convert the inventor's work in adapting his invention to the manufacturer's product into the work of a hired technician whose work product was automatically owned by the manufacturer.

[28] Federal Courts 644
170Bk644 Most Cited Cases
Although there was a hint in posttrial colloquy that court intended or was willing to retry all trade secret issues, that was not sufficient to excuse plaintiff from requesting, through posttrial motion, a new trial or judgment n.o.v. on certain trade secret issues when defendant sought new trial or judgment n.o.v. with respect to other trade secrets.

[29] Federal Courts 759.1
170Bk759.1 Most Cited Cases
(Formerly 170Bk759)
Appellate tribunal is abjured to determine whether jury verdict can be sustained on any reasonable theory.

[30] Damages 137
115k137 Most Cited Cases
Evidence sustained jury's award of $104,000 for motorcycle manufacturer's misappropriation of trade secrets of inventor of rear wheel suspension system.

[31] Patents 317
291k317 Most Cited Cases
Injunction will generally issue when any patent infringement has been adjudged, absent sound reason for denying the injunction.

[32] Patents 317
291k317 Most Cited Cases
Injunction against future patent infringement was proper where the patent would expire in less than four years, litigation had started over eight years earlier, and further proceedings could consume "several years.".

[33] Injunction 56
212k56 Most Cited Cases
Misappropriator of trade secrets has no authorization right to continue to reap the benefits of its wrongful acts, and owner of the trade secrets is entitled to injunction against continued use of the secrets by the misappropriator.

[34] Fraud 58(1)
184k58(1) Most Cited Cases
Evidence sustained finding of fraud on the part of manufacturer which misappropriated inventor's trade

secrets and infringed his patent.

[35] Federal Civil Procedure 2338.1
170Ak2338.1 Most Cited Cases
(Formerly 170Ak2338)
New trial is not warranted simply because the district court would have reached different verdict.

[36] Fraud 61
184k61 Most Cited Cases
Jury's assessment of punitive damages is not excluded in patent and trade secret cases where the jury expressly finds fraud.

[37] Patents 312(7)
291k312(7) Most Cited Cases
Evidence sustained finding that plaintiff in patent infringement action was not the "real inventor" of the patent in view of evidence that he invented the patent with another and in view of contribution of third parties.

[38] Patents 312(7)
291k312(7) Most Cited Cases
Fact that plaintiff in patent infringement action might have been only a joint inventor rather than a sole inventor did not affect issue of whether he was entitled to assignment of patent obtained by infringer of inventor's patent, as the correction of inventorship would be an administrative step, and was not before the court.

[39] Patents 323.1
291k323.1 Most Cited Cases
Inventor claiming that he was entitled to patent obtained by infringer of his patent was not limited to remedy of interference in the United States Patent and Trademark Office and in other countries, and could obtain court order assigning him the infringer's patent.

[40] Patents 312(6)
291k312(6) Most Cited Cases
Jury could have found that manufacturer's infringement of inventor's patent was willful. 35 U.S.C.A. § § 284, 285.

Patents 328(2)
291k328(2) Most Cited Cases
4,457,393. Cited.

Patents 328(2)
291k328(2) Most Cited Cases
3,907,332. Valid and Infringed.

***1229** Theresa A. Middlebrook, Wagner & Middlebrook, Glendale, Cal., and Robert W. Driscoll, Driscoll & Tomich, San Marino, Cal., argued for plaintiff/appellant. With them on the brief was John E. Wagner.

John A. Fogarty, Kenyon & Kenyon, New York City, argued for defendants/cross-appellants. With him on the brief were Richard S. Gresalfi and Dawn M. DiStefano. Also on the brief were Richard S. Rockwell, Tustin, Cal., Duffern H. Helsing and Halina F. Osinski, Santa Ana, Cal., of counsel.

Before SMITH, Circuit Judge, SKELTON, Senior Circuit Judge, and NEWMAN, Circuit Judge.

PAULINE NEWMAN, Circuit Judge.

This appeal and cross-appeal are from the judgment of the United States District Court for the Central District of California, and involve issues of patent validity, infringement, breach of contract, fraud, misappropriation ***1230** of trade secrets, and several related issues. [FN1] We affirm in part, reverse in part, vacate in part, and remand.

FN1. *Richardson v. Suzuki Motors Co. and Suzuki U.S. Motors Corp.*, Nos. CV 80-2589-WPG and CV 82-3826-WPG (C.D.Cal. June 29, 1987 and July 13, 1987).

The Invention

The invention that led to this litigation is a motorcycle rear-wheel suspension system that smooths the ride over rough terrain, of interest particularly in off-road motorcycle riding. The roughness of the ride is due to bumps and dips in the terrain, transmitted from the wheels to the frame. An optimum rear-wheel suspension will maintain tire contact with the ground despite deflection by irregularities, will avoid "bottoming out" (an unsafe rising of the suspension), yet will achieve a smooth ride without reduction in safety. In 1974 even the best available suspensions did not maintain adequate tire contact with the ground in conjunction with attempts to eliminate bottoming out.

In mid-1974 Donald G. Richardson, a young mechanic in California, devised a solution to the problem, a modified suspension system that he installed in his own motocross motorcycle. Richardson replaced the conventional two-spring shock absorber suspension system with a system consisting of a single shock absorber plus a linkage

consisting of a bell crank and connecting rod. This linkage generated a "rising rate" [FN2]--a characteristic critical to the issue--and produced a far superior ride, even as it eliminated the dangerous bottoming out. Richardson testified about his first ride, at a hilly construction site near his house, as "utopia. I mean it was incredible"; over hard bumps it was "uncanny because it was so smooth"; "[t]he rear end didn't kick up. It just didn't bottom out and stayed down"; an "unbelievable feeling".

> FN2. "Rising rate" was described by witnesses as follows: "as the suspension travels upward, the resistance to upward travel will increase"; and it "gets stiffer as the wheel moves up toward the vehicle or moves upward in the frame."

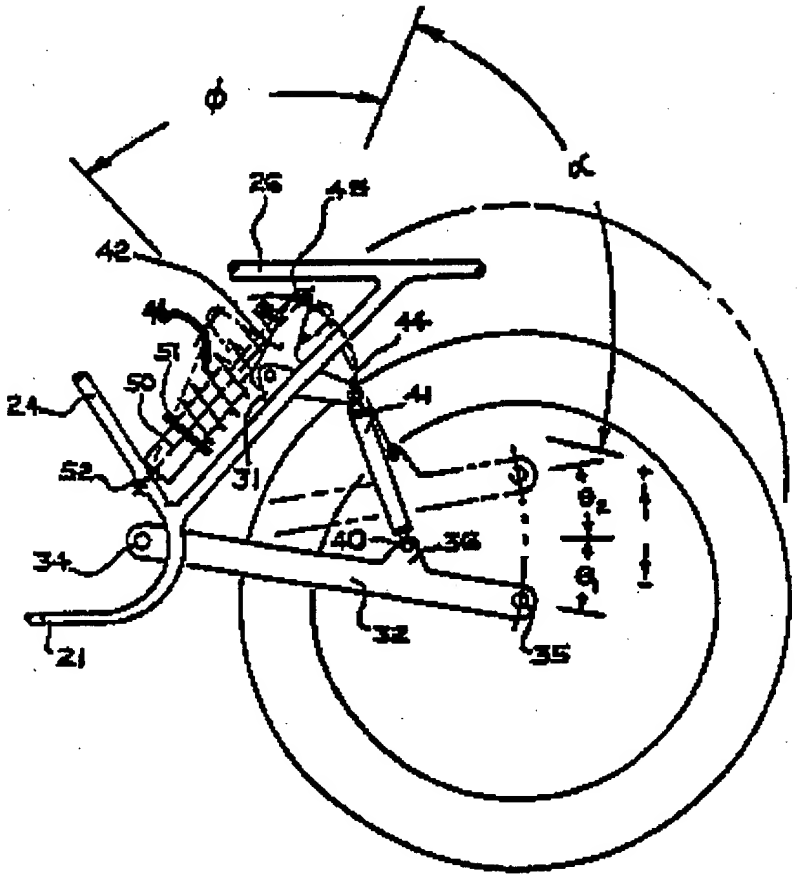
On November 25, 1974 Richardson filed a United States patent application on his invention, and on September 23, 1975 the application issued as United States Patent No. 3,907,332 (hereinafter the '332 or Richardson patent). Patent claim 9, which incorporates claim 1, is the only claim in suit. Claims 1 and 9 follow:

1. A suspension for two wheeled vehicles comprising:
a frame for the vehicle comprising a generally closed shape including upper and lower portions and
a swing arm pivotally connected to the lower portion of said frame;
said swing arm comprising a pair of arms rotatably supporting a wheel about a horizontal axis generally at the end of said swing arm;
the pivotal mounting of said arm to said frame being about a generally horizontal axis whereby said wheel is both rotatable about its own horizontal axis and deflectable in a generally vertical direction about the axis of said swing arm;
spring means having a first end pivotally secured to said frame;
a link member including an intermediate point pivotally mounted on said frame about an axis, parallel to the axis of said swing arm at a point spaced therefrom;
pivotal connection means between said link member and the second end of said spring;
a bar pivotally connected at one end to said swing arm and at the opposite end to said link member at a position spaced from said spring connection;
said spring, bar, swing arm and link connected whereby deflection of said swing arm displaces said bar and rotates said link member to compress said spring.

9. The combination in accordance with claim 1 wherein said assembly provides a rising spring rate as a function of deflection of said swing arm.

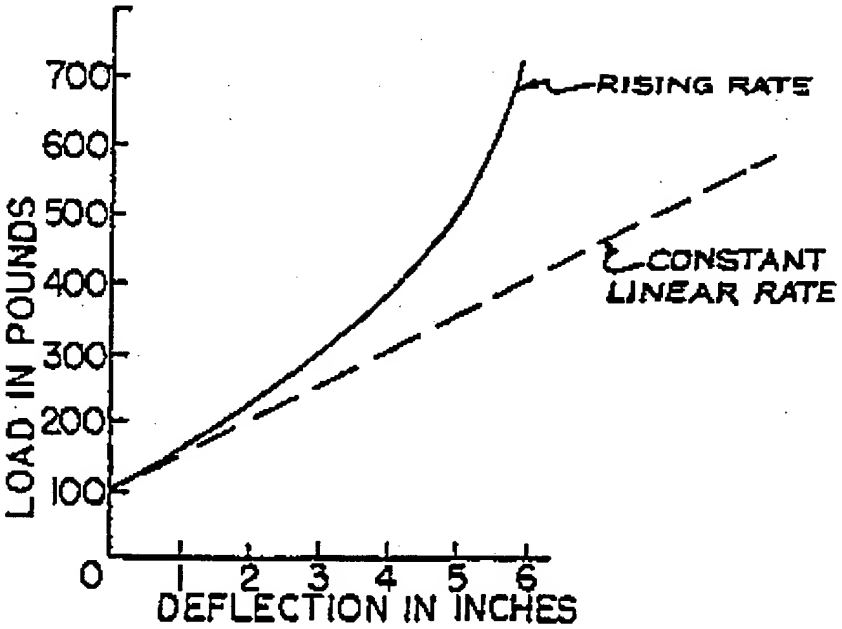
Figure 2 of the '332 patent specification is illustrative:

***1231**



As the rear wheel is deflected upward by bumps in the terrain, the swing arm (32) that is pivotally connected at (34) to the motorcycle frame (21) rotates upward, pushing the compression rod (41) into the bell crank (42) that is pivotally secured (31) at its intermediate point to the motorcycle frame. The bell crank rotates on its pivot (31) and compresses, downward against the frame, a spring (46) that is pivotally connected at one end (45) to the bell crank, and at its other end (52) to the motorcycle frame. The interaction of these interconnected parts increases the force on the spring, increasing the rate of resistance to deflection of the wheel with increased movement of the wheel. This varying resistance is the "rising spring rate" of claim 9, and is illustrated in Figure 5 of the '332 patent:

***1232**



The Contract with Suzuki

In October 1978 Richardson entered into a one year Option and License Agreement with the Suzuki Motor Co., Ltd. of Japan ("Suzuki").

The Agreement gave Suzuki the exclusive right to test and evaluate Richardson's suspension, and the exclusive option to acquire an exclusive license to the '332 patent and Richardson's "proprietary technical information, know-how, inventions, and use data", collectively defined in the Agreement as the "Licensed Rights."

The Agreement required Richardson to disclose to Suzuki all technical information, know-how, inventions, use data and design specifications for his suspension, that he possessed or that he acquired during the option period. Suzuki agreed to preserve all such information in confidence, and not to use any of it "for any purpose other than to evaluate for commercial feasibility of manufacture and marketing during the Option Period." Suzuki agreed that this obligation of confidence continued if Suzuki did not exercise the option. Excepted from the confidentiality obligation was all information previously known to Suzuki or at any time generally known to the public.

The Agreement required Richardson to make prototypes of his suspension system for Suzuki's evaluation. Richardson installed his suspension in Suzuki's sample 1978 and 1979 model production motorcycles, and disclosed to Suzuki the technical information and know-how that he possessed, including improvements and other information that he developed during this period. He met frequently with Suzuki engineers and other Suzuki personnel in the United States and in Japan to communicate this information and generally to improve performance and to facilitate testing and evaluation.

There was testimony at trial of initial incredulity on the part of Suzuki engineers concerning Richardson's suspension, of Suzuki's past failures in designing a suspension with the desired characteristics, and of Suzuki's favorable response to the performance of Richardson's suspension. The evidence included internal Suzuki documents made while Suzuki was testing Richardson's suspension, stating that it would "take a long time", perhaps three years, for Suzuki to develop a satisfactory suspension.

In early 1979 Richardson and a colleague Cazort conceived an improvement in the linkage-generated rising rate suspension, which they called the "Alternate Shock Mount" and which they disclosed to Suzuki, accompanied by drawings and blueprints ***1233** made by Cazort. The difference from the structure described in the '332 patent is that in the Alternate Shock Mount the lower end of the spring is pivotally secured to the swing arm which is pivotally secured to the frame, instead of being pivotally secured directly to the frame, resulting in increased strength.

In May 1979 Richardson's first prototype for Suzuki, wherein Richardson, aided by Cazort, installed his

suspension in a Suzuki 1978 production model, was successfully tested in Japan. Testimony at trial included statements attributed to Suzuki's test riders that they could see the bumps but not feel them, and other commentary evidencing a highly favorable reaction to Richardson's suspension.

It was a stipulated fact that after these tests Suzuki made the decision to place the linkage-generated rising rate suspension system into production, and started development work for this purpose.

On October 16, 1979 Suzuki filed a patent application in Japan. The corresponding United States patent, filed on October 8, 1980, claims the Alternate Shock Mount suspension as disclosed by Richardson, and also claims a modification made by Suzuki called the "criss-cross". Suzuki named two of its engineers, Hirohide Tamaki and Manabu Suzuki, as the inventors.

Suzuki twice requested and was granted one-month extensions of its Option and License Agreement with Richardson. In December 1979 Suzuki informed Richardson that it would not exercise the option.

In March 1980 Suzuki began competitive racing in the United States of Suzuki motorcycles using the Alternate Shock Mount suspension, which Suzuki named the "Full Floater". Suzuki met with marked racing success, the Full Floater receiving favorable publicity and high acclaim from the public. Extensive advertising was directed to the Full Floater rising rate suspension. The product achieved widespread commercial success.

Suzuki denied any obligation to Richardson.

Litigation

Richardson brought suit against Suzuki (Japan) and the U.S. Suzuki Motor Corporation in California state court, and was granted a preliminary injunction restraining the Suzuki companies from breach of the Option and License Agreement and requiring them to comply with the confidentiality terms thereof. At Suzuki's request the state court declined to enforce the injunction after U.S. Suzuki sued Richardson in federal court, seeking a declaratory judgment of invalidity and non-infringement of Richardson's '332 patent.

In 1982 Richardson filed a patent infringement action against the Suzuki companies and others. (Only the Suzuki companies remain as parties.) Richardson reasserted the state claims of breach of contract, breach of implied covenant of good faith and fair dealing, misappropriation of trade secrets, and fraud, and among other relief requested assignment of the patents obtained by Suzuki on the Alternate Shock Mount. Suzuki counterclaimed for fraud and breach of contract by Richardson, based on asserted invalidity of the '332 patent.

The federal actions were consolidated and tried to a jury. After forty-seven days of a two-part trial the jury gave special verdicts on issues of liability and damages. The district court entered final judgment under Fed.R.Civ.P. 54(b) on the jury verdicts that the '332 patent was not invalid and was infringed by Suzuki, that nine of Richardson's eleven asserted trade secrets were not trade secrets, and that Richardson was not entitled to assignment of the Tamaki/Suzuki patents on the Alternate Shock Mount. The court also entered final judgment on the jury verdicts of damages for patent infringement and for Suzuki's use of certain of Richardson's information that the jury found were not trade secrets. The court denied prejudgment interest and attorney fees, and refused to grant an injunction.

The district court denied most of the parties' post-trial motions, but granted Suzuki's motion for a new trial on three issues that the jury had decided in favor of ***1234** Richardson, upholding two of the eleven asserted trade secrets, finding fraud on the part of Suzuki, and assessing damages for fraud. The district court then entered a supplemental final judgment for immediate appeal of the issues that the court intended to retry, and certified three specific questions on these and related issues.

I

Validity of Richardson's '332 Patent

Suzuki asserts on appeal the invalidity of claim 9 on grounds of anticipation (35 U.S.C. § 102) and obviousness (35 U.S.C. § 103). [FN3] The district court, stating that questions of patent validity must be decided by the court, told the jury that its verdicts on this issue were advisory. Nevertheless the court duly entered the jury verdicts, including the answer YES to the question: "Under the facts and law as you believe that you understand them, do you find Claim 9 of the Richardson Patent to be valid?" The court entertained, and denied, post-trial motions for judgment n.o.v. and for a new trial on the question of validity. The court also independently decided the question, upholding validity of the '332 patent.

FN3. The additional aspects of adequacy of disclosure (35 U.S.C. § 112) and

> unenforceability for inequitable conduct, both decided in favor of Richardson, have not been appealed.

The record provided to us doesn't show the origin of this discredited procedure of advisory verdicts, or whether either party objected. In *Perkin-Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 895 n. 5, 221 USPQ 669, 674 n. 5, (Fed.Cir.), *cert. denied*, 469 U.S. 857, 105 S.Ct. 187, 83 L.Ed.2d 120 (1984), we observed that:

> The view suggested in *Sarkisian [v. Winn-Proof Corp.*, 688 F.2d 647, 651, (9th Cir.1982), *cert. denied*, 460 U.S. 1052 [103 S.Ct. 1499, 75 L.Ed.2d 930] (1983)], that a jury verdict on nonobviousness is at best advisory, would make charades of motions for directed verdict or JNOV under Fed.R.Civ.P. 50 in patent cases. These motions apply only to *binding* jury verdicts....
> Moreover, use of an advisory jury is limited to actions not triable of right by a jury.

(emphasis in original, citations omitted). In a similar circumstance wherein the trial court and the jury independently decided the same jury question (in that case the question of willfulness of infringement) we remarked that "[a]ll fact findings of a jury are non-advisory, unless made in an area expressly removed from jury verdict." *Shiley, Inc. v. Bentley Laboratories, Inc.*, 794 F.2d 1561, 1568, 230 USPQ 112, 115 (Fed.Cir.1986), *cert. denied*, 479 U.S. 1087, 107 S.Ct. 1291, 94 L.Ed.2d 148 (1987).

[1] It is established that the jury may decide the questions of anticipation and obviousness, either as separate special verdicts or en route to a verdict on the question of validity, which may also be decided by the jury. *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1547, 220 USPQ 193, 197 (Fed.Cir.1983):

> No warrant appears for distinguishing the submission of legal questions to a jury in patent cases from such submissions routinely made in other types of cases. So long as the Seventh Amendment stands, the right to a jury trial should not be rationed, nor should particular issues in particular types of cases be treated differently from similar issues in other types of cases.

See also, e.g., *Vieau v. Japax, Inc.*, 823 F.2d 1510, 1515, 3 USPQ2d 1094, 1098 (Fed.Cir.1987); *Verdegaal Brothers Inc. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1052 (Fed.Cir.), *cert. denied*, 484 U.S. 827, 108 S.Ct. 95, 98 L.Ed.2d 56 (1987); *Data Line Corp. v. Micro Technologies, Inc.*, 813 F.2d 1196, 1200, 1 USPQ2d 2052, 2054 (Fed.Cir.1987); *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1571, 1 USPQ2d 1081, 1085 (Fed.Cir.1986); *DMI, Inc. v. Deere & Co.*, 802 F.2d 421, 425-27, 231 USPQ 276, 279-80 (Fed.Cir.1986); *Mainland Industries, Inc. v. Standal's Patents Ltd.*, 799 F.2d 746, 747-48, 230 USPQ 772, 773 (Fed.Cir.1986); ***1235***Trans-World Mfg. Corp. v. Al Nyman & Sons, Inc.*, 750 F.2d 1552, 1560, 224 USPQ 259, 263 (Fed.Cir.1984); *Quaker City Gear Works, Inc. v. Skil Corp.*, 747 F.2d 1446, 1454-55, 223 USPQ 1161, 1165-66 (Fed.Cir.1984), *cert. denied*, 471 U.S. 1136, 105 S.Ct. 2676, 86 L.Ed.2d 694 (1985); *Weinar v. Rollform Inc.*, 744 F.2d 797, 805, 223 USPQ 369, 372 (Fed.Cir.1984), *cert. denied*, 470 U.S. 1084, 105 S.Ct. 1844, 85 L.Ed.2d 143 (1985); *Perkin-Elmer Corp.*, 732 F.2d at 894-95, 221 USPQ at 674; *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758, 221 USPQ 473, 477 (Fed.Cir.1984); *Railroad Dynamics, Inc. v. A. Stucki Company*, 727 F.2d 1506, 1512-13, 220 USPQ 929, 935 (Fed.Cir.), *cert. denied*, 469 U.S. 871, 105 S.Ct. 220, 83 L.Ed.2d 150 (1984); *White v. Jeffrey Mining Mach. Co.*, 723 F.2d 1553, 1558, 220 USPQ 703, 705 (Fed.Cir.1983) ("Submission of such a question of law [obviousness] to a jury, accompanied by appropriate instructions, is proper."), *cert. denied*, 469 U.S. 825, 105 S.Ct. 104, 83 L.Ed.2d 49 (1984). *See generally* H.T. Markey in *On Simplifying Patent Trials*, 116 F.R.D. 369, 370 (1987) ("There is neither reason nor authority for employing in a patent trial procedures and practices different from those employed in any other civil trial. Indeed, reason and authority mandate the contrary.")

[2] Although the district court and the jury reached the same result, the standards by which appellate courts review the judgment differ, depending on whether it arose from a jury or a bench trial. *District of Columbia v. Pace*, 320 U.S. 698, 701, 64 S.Ct. 406, 408, 88 L.Ed. 408 (1944) ("findings of fact by an equity court and the verdict of a jury have from time immemorial been subject to different rules of finality"). When the judgment arises from a jury verdict, the reviewing court applies the reasonable jury/substantial evidence standard: a standard that gives greater deference to the judgment simply because appellate review is more limited, compared with review of a trial judge's decision. *Id.* at 702, 64 S.Ct. at 408. As summarized in *Lavender v. Kurn*, 327 U.S. 645, 653, 66 S.Ct. 740, 744, 90 L.Ed. 916 (1946), "the appellate court's function is exhausted when that evidentiary basis [of the jury's verdict] becomes apparent, it being immaterial that the court might draw a contrary inference or feel that another conclusion is more reasonable." *See generally* M.B. Louis, *Allocating Adjudicative Decision Making Authority Between the Trial and Appellate Levels: A*

Unified View of the Scope of Review, The Judge/Jury Question, and Procedural Discretion, 64 N.C.L.Rev. 993 (1986).

The parties do not take a position on the district court's procedure, but appear to recognize that the issue of validity was properly for jury determination, for neither party refers to the district court's explanation of its independent determination of the question of obviousness.

In the interest of reaching an end to this protracted litigation, we have reviewed the judgment on the terms on which it reaches us. We have determined first whether Suzuki met its burden of showing on appeal that no reasonable jury could have reached the verdict of "valid" on the evidence before it. *Allen Organ Co. v. Kimball Int'l, Inc.,* 839 F.2d 1556, 1566, 5 USPQ2d 1769, 1777 (Fed.Cir.), *cert. denied,* 488 U.S. 850, 109 S.Ct. 132, 102 L.Ed.2d 104 (1988); *DMI, Inc. v. Deere & Co.,* 802 F.2d 421, 425, 231 USPQ 276, 278 (Fed.Cir.1986); *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.,* 758 F.2d 613, 618-19, 225 USPQ 634, 636 (Fed.Cir.), *cert. dismissed,* 474 U.S. 976, 106 S.Ct. 340, 88 L.Ed.2d 326 (1985). Then, on the premise that the parties may have waived their right to a jury trial on this question by failure to object to the district court's procedure, we have considered whether the district court's independent judgment of validity may be sustained, on the standards applicable thereto. *Panduit Corp. v. Dennison Mfg. Co.,* 810 F.2d 1561, 1566-68, 1 USPQ2d 1593, 1595-97 (Fed.Cir.) (obviousness determination in bench trial reviewed as a question of law based on underlying facts), *cert. denied,* 481 U.S. 1052, 107 S.Ct. 2187, 95 L.Ed.2d 843 (1987).

The court correctly instructed the jury that invalidity must be proved by clear and convincing evidence, referring to the presumption of validity. ***1236***Perkin-Elmer Corp.,* 732 F.2d at 894, 221 USPQ at 674; *Jamesbury Corp. v. Litton Industrial Products, Inc.,* 756 F.2d 1556, 1559, 225 USPQ 253, 255 (Fed.Cir.1985); *American Hoist & Derrick Co. v. Sowa & Sons, Inc.,* 725 F.2d 1350, 1360, 220 USPQ 763, 771 (Fed.Cir.), *cert. denied,* 469 U.S. 821, 105 S.Ct. 95, 83 L.Ed.2d 41 (1984).

A. Anticipation

[3][4] The district court correctly instructed the jury that an invention is anticipated if the same device, including all the claim limitations, is shown in a single prior art reference. Every element of the claimed invention must be literally present, arranged as in the claim. *Perkin-Elmer Corp.,* 732 F.2d at 894, 221 USPQ at 673; *Kalman v. Kimberly-Clark Corp.,* 713 F.2d 760, 771-72, 218 USPQ 781, 789 (Fed.Cir.1983), *cert. denied,* 465 U.S. 1026, 104 S.Ct. 1284, 79 L.Ed.2d 687 (1984). The identical invention must be shown in as complete detail as is contained in the patent claim. *Jamesbury Corp.,* 756 F.2d at 1560, 225 USPQ at 256; *Connell,* 722 F.2d at 1548, 220 USPQ at 198.

As prior art, Suzuki relied on the motorcycle suspensions described in certain patents to Downs and Warner, and on the race car wheel suspensions described for Tyrrell and McLaren race cars in two Road and Track magazine articles. Witnesses explained to the jury the similarities and differences between the invention of the '332 patent and each prior art reference. For example, the Downs suspension has a spring element that is rigidly attached to the motorcycle frame and does not pivot as is required by claim 9 of the '332 patent. The Warner reference shows a suspension having a bell crank that is pivotally mounted to the motorcycle frame but not at an intermediate point, whereas Richardson requires a mid-point pivot of the bell crank to the frame. Neither Downs nor Warner describes a rising rate. The magazine articles describe a four wheel racing car suspension system having a linkage-generated variable rising rate incorporating a bell crank, but instead of the swing arm of Richardson's motorcycle suspension, the race car systems use an A-shaped arm mounted to the side of an upright wheel; and the bell crank and linkage in the race car system is located beside the wheel, rather than in front of the wheel as in Richardson's motorcycle system.

Witnesses testified that rising rate in motorcycles had previously been obtained only by progressively wound springs and gas operated shock absorbers. Suzuki argued that rising rate is inherent in the Downs and Warner motorcycle suspensions and expressly described for race cars in the magazine articles, and also that rising rate is merely a statement of function, and thus should not be a basis for distinction from the prior art.

The jury found that Downs did not "disclose each and every element of the Richardson Claims 1 and 9 or their equivalent". For the Warner reference, the jury could not reach a unanimous verdict on this same question, but answered NO to the question whether "the respective elements of Warner function in substantially the same way as the corresponding elements in Richardson to produce substantially the

same results". The jury found that the race car suspensions did "disclose each and every element of the Richardson Claims 1 and 9 or their equivalent", but did not reach a unanimous verdict as to whether they "function in substantially the same way as the corresponding elements in Richardson to produce substantially the same results."

[5] The jury had erroneously been instructed that anticipation may be shown by equivalents, a legal theory that is pertinent to obviousness under Section 103, not to anticipation under Section 102. *Lewmar Marine, Inc. v. Barient, Inc.*, 827 F.2d 744, 747-48, 3 USPQ2d 1766, 1768 (Fed.Cir.1987), *cert. denied*, 484 U.S. 1007, 108 S.Ct. 702, 98 L.Ed.2d 653 (1988); *Connell*, 722 F.2d at 1548, 220 USPQ at 198. The jury requested a definition of "equivalent" during its deliberations, and was given the Webster's dictionary definition "corresponding or virtually identical, especially in effect or function." This narrow definition, which does not accord with that of *1237*Graver Tank & Mfg. Co. v. Linde Air Products Co.*, 339 U.S. 605, 608, 70 S.Ct. 854, 856, 94 L.Ed. 1097 (1950), may have minimized the legal error in the instructions. In any event, the erroneous inclusion of equivalents in the anticipation inquiry favored Suzuki. The jury nonetheless answered YES to the special verdict: "Under the facts and law as you believe that you understand them, do you find Claim 9 of the Richardson Patent to be valid?"

[6] On the totality of the evidence and in light of the jury instructions and answers, we conclude that a reasonable jury could have found that the patent was not invalid on grounds of anticipation. *Perkin-Elmer Corp.*, 732 F.2d at 894, 221 USPQ at 673-74 (review of presumed jury finding that anticipation not proved, based on jury verdict of validity).

Reviewing the analysis and decision of the district court, based on the same prior art, we discern no clear error in the court's conclusion that claim 9 was not invalid.

We affirm that claim 9 was not proved invalid on the ground of anticipation.

B. Obviousness

The issue of obviousness was vigorously litigated, Suzuki relying on the same Downs and Warner patents and magazine articles. The record shows that there was extensive testimony concerning the differences between Richardson's suspension and the prior art. Suzuki argued at trial, and repeats on this appeal, that these differences are trivial mechanical expedients.

The jury, among its special verdicts on the *Graham* factors, found that a person of ordinary skill in the pertinent art could be any of: (1) a motorcycle mechanic without formal technical education, (2) a person with experience in working on suspension systems for racing automobiles, but without formal technical training, (3) suspension system instructors, (4) professional motorcycle riders, and (5) someone possessing above-average mechanical skills. Suzuki argues that such a person is of generally high mechanical skill, and to such a person Richardson's rising rate motorcycle suspension would have been an obvious "adaption" of the race car suspension systems, which "suggests itself quite plainly, since Downs and Warner incorporate bell cranks in their respective suspensions."

The jury was unable to reach a unanimous verdict on the question of whether a person of the level of skill found by the jury, presented with the problem and being familiar with all the prior art including these four specific references, but unaware of Richardson's device, would be "led to do" what Richardson did. In response to the ultimate question, as we have observed, the jury reached the unanimous verdict that "Under the facts and law as you believe that you understand them", claim 9 was "valid". The district court entered judgment on the jury verdicts, independently held the patent valid, and denied Suzuki's motions for judgment n.o.v. and for a new trial on the issue of validity.

[7] The question for the jury was whether the challenger met the burden of proving invalidity by clear and convincing evidence; and the question on review is whether reasonable jurors could have concluded that the challenger failed to meet that burden. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1571, 1 USPQ2d 1081, 1085 (Fed.Cir.1986); *Perkin-Elmer Corp.*, 732 F.2d at 894-95, 221 USPQ at 674. The jury's lack of unanimity on certain special verdicts can reasonably be taken to mean, as the district court held, that invalidity had not been proved by clear and convincing evidence.

[8][9] Our review shows that there was substantial evidence on which reasonable jurors could have concluded that claim 9 had not been proved invalid for obviousness, and thus reached the verdict of "valid". Although the district court erred in its belief that obviousness could only be presented to the jury for an advisory verdict, we may view the court's agreement with the jury verdict of validity as

supporting the court's denial of Suzuki's post-trial motions for judgment n.o.v. and for a new trial. *Perkin-Elmer Corp.*, 732 F.2d at 895, 221 USPQ at 674-75. However it is viewed procedurally, no reversible error ***1238** has been shown in the court's conclusion that obviousness had not been proved and that claim 9 was not invalid.

The judgment of validity is affirmed.

II

Infringement

[10][11] Richardson bore the burden of proving infringement by a preponderance of the evidence. The district court correctly stated that the jury was the finder of the fact of infringement.

[12] The jury rendered special verdicts as to the Suzuki motorcycles before it, Model M having the Richardson/Cazort Alternate Shock Mount and Model C having the "criss-cross" connection added by Suzuki, as follows:

> 9(a). Do defendant Suzuki's motorcycles of the Model M type ... infringe Claim 9 of the plaintiff's patent?
>
> Answer: YES, WITH THE RISING RATE
>
> 9(b). Do defendant Suzuki's motorcycles of the Model C type ... infringe Claim 9 of the plaintiff's patent?
>
> Answer: YES, WITH THE RISING RATE

In subparts 9(a)(2) and 9(b)(2) of the special verdict the jury answered YES to the question whether the Suzuki motorcycles produce substantially the same rising rate as taught in Richardson's patent.

The principal question on appeal is the meaning and effect of the jury answers to subparts (1) of the special verdict, which were directed "in particular" to the Alternate Shock Mount and the criss-cross modifications:

> 9(a)(1). In particular, is the defendant's linkage equivalent to the plaintiff's, bearing in mind that the bottom of the spring in the former is affixed to the swing arm rather than to the frame?
>
> Answer: NO
>
> 9(b)(1). In particular, is the defendant's linkage equivalent to the plaintiff's, in light of the "criss-cross" of the connecting rods and the bell crank in the defendant's model, as well as the spring attachment to the swing arm, as compared with the plaintiff's Claim 9?
>
> Answer: NO

The district court entered judgment of infringement in favor of Richardson and denied post-trial motions by both sides, including a motion by Richardson to reopen the record in order to present evidence on the doctrine of equivalents. The district court stated that the jury verdicts mean that "infringement is limited to 'rising rate' " and that the Suzuki and Richardson linkages are not equivalent.

Suzuki argues that special verdicts 9(a)(1) and 9(b)(1) require judgment of non-infringement; or, as a minimum, that these verdicts are inconsistent with the verdicts of infringement in 9(a) and 9(b), such that a new trial is required of the entire issue. Richardson states that the verdicts can be understood, when viewed in light of the jury instructions, in a way that supports the judgments of infringement. Suzuki did not request a new trial on the basis of inconsistent verdicts at the time the judgments were entered, while Richardson moved, unsuccessfully, to amend or delete verdicts 9(a)(1) and 9(b)(1). Each party asserts that any inconsistency should be resolved in its favor.

The Ninth Circuit, in accordance with the general rule, requires trial and appellate courts to seek reconciliation of apparently inconsistent verdicts:

> When faced with a claim that verdicts are inconsistent, the court must search for a reasonable way to read the verdicts as expressing a coherent view of the case, and must exhaust this effort before it is free to disregard the jury's verdict and remand the case for a new trial.

Toner v. Lederle Laboratories, 828 F.2d 510, 512 (9th Cir.1987), *cert. denied*, 485 U.S. 942, 108 S.Ct. 1122, 99 L.Ed.2d 282 (1988) (citing *Gallick v. Baltimore & Ohio R.R.*, 372 U.S. 108, 119, 83 S.Ct. 659, 666, 9 L.Ed.2d 618 (1963), also citing *Atlantic & Gulf Stevedores, Inc. v. Ellerman Lines, Ltd.*, 369 U.S. 355, 364, 82 S.Ct. 780, 786, 7 L.Ed.2d 798 (1962) and *Blanton v. Mobil Oil Corp.*, 721 F.2d 1207, 1213, (9th Cir.1983), *cert. denied*, ***1239**471 U.S. 1007, 105 S.Ct. 1874, 85 L.Ed.2d 166 (1985)). *See also Allen Organ Co.*, 839 F.2d at 1563, 5 USPQ2d at 1775 (the appellate court must make every effort to harmonize the jury's answers).

The district court did not find the special verdicts inconsistent, apparently in the belief that the jury limited infringement to the rising rate provision of claim 9 but not the other claim clauses. This accords with the court's statement to the jury that the infringement was "minor" because it was limited to the rising rate. This interpretation pleased neither party. If we have correctly understood it, it is incorrect as a matter of law.

"We are bound to find the special verdicts consistent if we can do so under a fair reading of them." *Toner*, 828 F.2d at 512. A fair reading of the special verdicts results from simply applying the rule that "[t]he consistency of the jury verdicts must be considered in light of the judge's instructions to the jury". *Toner*, 828 F.2d at 512. The instructions on infringement, and the specific questions asked by special verdict, were designed to resolve the issues raised at trial. There was testimony on both sides of Suzuki's assertion that its suspension was not the same as Richardson's because it produced a different rising rate. We referred *supra* to special verdicts 9(a)(2) and 9(b)(2):

> 9(a)(2). Does defendant's Model M produce rising rate substantially the same as the rising rate produced under the teachings of the plaintiff's patent?
> Answer: YES
> 9(b)(2). Does defendant's Model C produce rising rate substantially the same as the rising rate produced under the teachings of the plaintiff's patent?
> Answer: YES

Another special verdict in the infringement section asked the jury:

> 11. Does claim 9 of the Richardson Patent describe the invention of a rising rate in terms of what the invention will do rather than in terms of physical arrangement?
> Answer: NO

We conclude that the answer "yes, with the rising rate" in verdicts 9(a) and 9(b) is the jury's response to Suzuki's argument, rather than as a finding that only the rising rate claim limitation, and no other, is embodied in the Suzuki suspensions.

We discern no support in the record for the district court's conclusion that verdicts 9(a) and 9(b) meant that the rising rate was the only area of infringement. Structure corresponding to every element of every clause of claims 1 and 9 was identified by witnesses as embodied in the accused motorcycles. There was no real dispute that of the nine or eleven elements in these claims (depending on how counted), all but one were literally present. The dispute centered on one element, the attachment of the spring in the claim clause "spring means having a first end pivotally secured to said frame", since this was the clause affected by the modifications of the Alternate Shock Mount and the criss-cross. In the Alternate Shock Mount, as we have discussed, the spring is pivotally secured to a swing arm that in turn is pivotally secured to the frame, instead of being pivotally secured directly to the frame as is shown in the '332 specification.

Richardson argues that the spring can be either directly or indirectly pivotally secured to the frame, without avoiding literal infringement of the claim. Richardson alternatively argues that on a correct definition of the doctrine of equivalents, citing *Graver Tank*, 339 U.S. at 608, 70 S.Ct. at 856, these securements are equivalent because the structures are substantially the same and perform substantially the same function in the same way.

The jury had been given the dictionary definition that "equivalent" means "corresponding or virtually identical, especially in effect or function". This definition was reinforced by the phrasing of verdicts 9(a)(1) and 9(b)(1), wherein the question itself instructed the jury on the difference between the linkages, while remaining silent on the similarities.

[13] This presentation was highly prejudicial. Indeed, these verdicts well illustrate the truism that the way a question is ***1240** asked can direct the answer. "The decision to submit interrogatories, and the precise language in which they are couched, can have an untoward effect on a verdict, if certain elements of the trial or the evidence are thereby overly emphasized in the jury's mind." *Weinar v. Rollform Inc.*, 744 F.2d 797, 809, 223 USPQ 369, 376 (Fed.Cir.1984),*cert. denied*, 470 U.S. 1084, 105 S.Ct. 1844, 85 L.Ed.2d 143 (1985).

[14] Further, and equally prejudicial, special verdicts 9(a)(1) and 9(b)(1) isolated this specific claim element so that it was removed from the perspective that is obtained only when the claimed invention is viewed in its entirety. *See, e.g., Hughes Aircraft Co. v. United States*, 717 F.2d 1351, 1363, 219 USPQ 473, 482 (Fed.Cir.1983). We recently reemphasized in *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1253 (Fed.Cir.1989), in discussing *Graver Tank*, that there is no error in considering "the principle of the claimed invention".

[15] A device that embodies improvements on a claimed structure does not automatically avoid the reach of the claim. *See, e.g., Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1580, 224 USPQ 409, 417 (Fed.Cir.1984) (separately patentable improvement may also be an equivalent under the doctrine of equivalents); *A.B. Dick Co. v. Burroughs Corp.*, 713 F.2d 700, 703, 218 USPQ 965, 967-68 (Fed.Cir.1983) (infringement not avoided "merely by adding elements"), *cert. denied*, 464 U.S.

1042, 104 S.Ct. 707, 79 L.Ed.2d 171 (1984). Each case must be decided on its particular facts, viewing the changes in the accused structure in light of the claimed invention. *See generally Pennwalt Corp. v. Durand-Wayland, Inc.*, 833 F.2d 931, 934-35, 4 USPQ2d 1737, 1739 (Fed.Cir.1987), *cert. denied*, 485 U.S. 961, 108 S.Ct. 1226, 99 L.Ed.2d 426 (1988), and *cert. denied*, 485 U.S. 1009, 108 S.Ct. 1474, 99 L.Ed.2d 703 (1988); *Texas Instruments, Inc. v. United States Int'l Trade Comm'n*, 805 F.2d 1558, 1569-70, 231 USPQ 833, 840 (Fed.Cir.1986), *reh'g denied*, 846 F.2d 1369, 6 USPQ2d 1886 (Fed.Cir.1988).

[16] We conclude that the jury verdicts, viewed in light of the instructions, held that the Suzuki motorcycles with a rising rate infringed claim 9. We also conclude that on correct instructions no reasonable jury could have found that the claimed invention and the accused structures are not equivalent, on the established facts of record, applying the correct law of *Graver Tank*. *See Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 252, 106 S.Ct. 2505, 2512, 91 L.Ed.2d 202 (1986) ("The mere existence of a scintilla of evidence in support of the plaintiff's position will be insufficient; there must be evidence on which the jury could reasonably find for the plaintiff."); *Pullman-Standard v. Swint*, 456 U.S. 273, 291-92, 102 S.Ct. 1781, 1791-92, 72 L.Ed.2d 66 (1982) ("where findings [by the district court] are infirm because of an erroneous view of the law, a remand is the proper course unless the record permits only one resolution of the factual issue"); *Dana Corp. v. IPC Limited Partnership*, 860 F.2d 415, 419, 8 USPQ2d 1692, 1696 (Fed.Cir.1988) (when there are sufficient established facts of record, appellate court has discretion to determine the merits of JNOV motion.)

The jury verdicts of infringement are supported by substantial evidence, and are upheld. The judgment of infringement is affirmed.

III

Damages for Patent Infringement

[17] As damages for patent infringement the jury assessed a royalty of fifty cents per motorcycle. Richardson states that this royalty is unreasonably low, and resulted from erroneous and prejudicial jury instructions. We review the award on the reasonable jury/substantial evidence standard. *Shatterproof Glass Corp.*, 758 F.2d at 627-28, 225 USPQ at 643-44.

[18] The court told the jury: "Now, I will sustain, I will uphold your verdict [of infringement], but in determining damages and determining any royalty, it seems to me that you must consider that the infringement was a relatively minor infringement." ***1241** This instruction derived, as we have discussed, from the erroneous interpretation of the verdicts as limited to the "rising rate" clause. We must determine whether this erroneous instruction was prejudicial to the jury's assessment of damages. The Ninth Circuit has stated that "we will reverse a judgment because of a mistake in jury instructions only if the error was prejudicial." *Smiddy v. Varney*, 665 F.2d 261, 265 (9th Cir.1981), *cert. denied*, 459 U.S. 829, 103 S.Ct. 65, 74 L.Ed.2d 66 (1982).

35 U.S.C. § 284 provides that damages shall be "adequate to compensate for the infringement, but in no event less than a reasonable royalty for the use made of the invention by the infringer". *Fromson v. Western Litho Plate and Supply Co.*, 853 F.2d 1568, 1574, 7 USPQ2d 1606, 1612 (Fed.Cir.1988). The jury was told that a royalty of $2.00 per motorcycle with an annual minimum of $70,000 had been agreed to by Suzuki and Richardson in the Option and License Agreement. There was testimony of much higher royalties paid by others for similar contributions to motorcycles. Suzuki presented testimony that the $2.00 in the agreement does not apply, but should be the starting point for reducing the royalty because the infringement was minor.

We must assume that the jury followed the court's instruction that the infringement was minor. That instruction was a misinterpretation of the jury verdict of infringement, and it usurped the role of the jury. Absent this prejudicial instruction there was no reasonable basis on which reasonable jury could have found that fifty cents was a reasonable royalty.

The judgment of damages for patent infringement is vacated. We remand for retrial of the question.

IV

Richardson's Technical Information

Issues relating to Richardson's technical information were presented at trial on the legal theories of breach of contract and the tort of misappropriation of trade secrets. The district court concentrated the tort issues in presentation to the jury, apparently accepting Suzuki's position that it had complied with its contractual obligations to Richardson. The court thus required that Richardson prove the existence of legally protectible trade secrets and their misappropriation by Suzuki.

In the only special verdict on the contract issues, the jury found that Suzuki did not violate its duty of good faith and fair dealing in its relationship with Richardson. The jury instructions on the contractual relationship, however, are pertinent to, and intertwined with, the trade secret issues.

A. The Contractual Relationship

[19] In matters of contract law and interpretation we apply the discernable law of the state of California. *Universal Gym Equipment, Inc. v. ERWA Exercise Equipment Ltd.*, 827 F.2d 1542, 1550, 4 USPQ2d 1035, 1040 (Fed.Cir.1987). At trial Richardson pressed, unsuccessfully, the California law that a covenant of good faith and fair dealing is implied between parties to a contract. *Seaman's Direct Buying Service, Inc. v. Standard Oil Co.*, 36 Cal.3d 752, 768, 686 P.2d 1158, 1166, 206 Cal.Rptr. 354, 363 (1984) ("It is well settled that, in California, the law implies in *every* contract a covenant of good faith and fair dealing." (Emphasis in original)).

The contract between Richardson and Suzuki was explained at trial, including the clause wherein Suzuki agreed not to use or disclose the "technical information, know-how, inventions, use data, and design specifications" that it received from Richardson. In discussing whether Suzuki was restrained in its post-contract use of Richardson's information, the district court at first instructed the jury that Suzuki was entitled by law "to use the most efficient means, even though they got it from plaintiff", stating that only "valid trade secrets" were subject to the contractual restraints:

> And then after Suzuki's election not to take a license, of course, they were not supposed to use the plaintiff's trade secrets. That's what the contract says. And once again, you're going to have to determine whether these eleven were val***1242** id trade secrets. To what extent did the defendant use them, to what extent would the defendant otherwise have developed them.
>
> Now, some of these trade secrets refer to the best alignments and designs. Well, it seems incongruous to say to the defendant they cannot use the best because the best was intentionally disclosed by the plaintiff, and even though experimentation by the defendant surely would have revealed the best as the patent says that it would.
>
> Were the defendants precluded from using the best or were they obliged to use something less efficient. I can't conceive of the defendants not being entitled to use the most efficient means, even though they got it from the plaintiff.

The court later qualified this position by referring to reverse engineering as being improper--although it is far from clear what a reasonable jury would have understood from the court's instructions:

> But on further reflection, I have to acknowledge that if you find there was a confidential relationship or contract that prohibited Suzuki from using the plaintiff's trade secrets, technical information or know-how, inventions or use data that the plaintiff gave them, unless it exercised the option, if you find those things to be true, I suppose it would be improper for Suzuki to reverse engineer from Richardson's prototypes, or from trade secrets or other information that he gave them.
>
> The defense of reverse engineering does not apply to information received in confidence or whereas here the information is given under a contract.

Reviewing these instructions in the context of the contract and trade secret questions that were before the jury, we conclude that the jury was incorrectly instructed on the law. *See Bulgo v. Munoz*, 853 F.2d 710, 714 (9th Cir.1988) (quoting *Los Angeles Memorial Coliseum Comm'n v. National Football League*, 726 F.2d 1381, 1398 (9th Cir.), *cert. denied*, 469 U.S. 990, 105 S.Ct. 397, 83 L.Ed.2d 331 (1984)) (instructions reviewed to determine "whether, viewing the jury instructions as a whole, the trial judge gave adequate instructions on each element of the case to ensure that the jury fully understood the issues.")

In *Universal Gym Equipment*, 827 F.2d at 1549, 4 USPQ2d at 1040, we affirmed liability under California law based on breach of contract, when the parties contracted to limit the use by the recipient of "features, designs, technical information, or know-how" disclosed under the contract. We also affirmed that such a contractual arrangement is not incompatible with the patent law, *id.* at 1550, 4 USPQ at 1041, an issue on which the district court in Richardson's case also appears to have been misled, and to have misled the jury. *See Components for Research, Inc. v. Isolation Products, Inc.*, 241 Cal.App.2d 726, 730, 50 Cal.Rptr. 829, 832 (1966) ("The judgment here but affords protection against the use of plaintiff's trade secrets by those to whom they had been disclosed in confidence. Whether the idea was patented or not, plaintiff is entitled to such protection").

The district court erred in law, in limiting the scope of protected information beyond that set forth in the contract, and in its instructions to the jury as to Suzuki's obligations. These errors are reflected in

the trade secret issues.

B. The trade secret issues

The jury, despite the excessively restrictive instructions on what were trade secrets, found that certain items that Suzuki had received from Richardson were trade secrets and had been misappropriated, and assessed damages therefor. The jury also assessed damages for use by Suzuki of certain other items that did not "rise to the dignity of trade secrets", in the words of the special verdicts.

Richardson specified eleven items that he had disclosed to Suzuki under the contract, and that he asserted to be trade secrets; to wit: (1) the optimal characteristics of a motorcycle rear-wheel suspension shock absorber, showing three external adjustments, (2) engineering drawings of his proposed and furnished suspension systems, ***1243** (3) 1978 and 1979 Suzuki motorcycles modified by Richardson with his rising rate suspension, (4) specific force-velocity curves needed to obtain the advantages of Richardson's invention in Suzuki's motorcycles, (5) design modifications to extend rear wheel travel over earlier rising-rate designs, (6) design of the Alternate Shock Mount including drawings and knowhow, (7) the optimum use and types of certain bearings in the suspension, (8) motorcycle testing and tuning criteria, (9) his bell crank designs and design criteria, (10) adjustments in the angles and dimensions of the parts of the suspension and their effect on performance, and (11) the straight line tubular motorcycle frame.

The California law of trade secrets follows the Restatement definition:

> A trade secret may consist of any formula, pattern, device or compilation of information which is used in one's business, and which gives him an opportunity to obtain an advantage over competitors who do not know or use it.... Generally it relates to the production of goods, as, for example, a machine or formula for the production of an article.

By-Buk Co. v. Printed Cellophane Tape Co., 163 Cal.App.2d 157 at 166, 329 P.2d 147 at 152, 118 USPQ 550 at 553, (1958) citing Restatement (First) of Torts, § 757 comment b (1939). The court in *By-Buk Co.* reaffirmed "plaintiff's right not to have its [trade secret] processes wrongfully disclosed to others and used to its detriment." *Id.* at 167, 329 P.2d at 153, 118 USPQ at 553.

[20][21] The burden of proof was placed on Richardson to prove that his information met the legal requirements of a protectible trade secret. *Forro Precision, Inc. v. International Business Machines Corp.*, 673 F.2d 1045, 1056-57, 215 USPQ 299, 305-6 (9th Cir.1982). This in turn required "either a covenant or a confidential relationship" as a premise of relief. *Futurecraft Corp. v. Clary Corp.*, 205 Cal.App.2d 279, 283, 23 Cal.Rptr. 198, 207-08 (1962) (discussing elements of trade secret protection). Richardson met this requirement through his contractual covenant.

[22] The district court told the jury, several times, that because Suzuki might have developed or could have developed on its own the information it received from Richardson, such information can not be protected as a trade secret. The court said: "Now I think we must assume that the defendant could have accomplished whatever the plaintiff may have contributed toward the development of Models M and C." Whatever the validity of the proposed assumption as to Suzuki's abilities, the court's conclusion is contrary to California law:

> It is not necessary in order that a process of manufacture be a trade secret that it be patentable or be something that could not be discovered by others by their own labor and ingenuity.

By-Buk Co., 163 Cal.App.2d at 166, 329 P.2d at 152, 118 USPQ at 553. Nor does the possibility of independent discovery relieve Suzuki of liability:

> "[S]ecret formulas and processes * * * are property rights which will be protected by injunction, not only as against those who attempt to disclose or use them in violation of confidential relations or contracts express or implied, but as against those who are participating in such attempt with knowledge of such confidential relations or contract, though they might in time have reached the same result by their own independent experiments or efforts."

Id. at 167, 329 P.2d at 153, 118 USPQ at 553-54 (quoting *Herold v. Herold China & Pottery Co.*, 257 F. 911, 913 (6th Cir.1919)). Indeed, Suzuki did not argue that it had actually developed on its own the information that it first received from Richardson. Although Richardson adduced evidence that Suzuki had been unable to solve this problem, it is not relevant what Suzuki might have been able to do on its own. Ninth Circuit law upholds trade secret status even had the same information been obtainable from other sources. *Clark v. Bunker*, 453 F.2d 1006, 1010, 172 USPQ 420, 423 (9th Cir.1972) (trade secrecy "is not negated because defendant by an expenditure of effort might have collected the ***1244** same information from sources available to the public.") (footnote omitted).

[23] The court also erroneously instructed the jury that "slavish" copying is necessary for misappropriation, and that an exercise of independent judgment would remove the information from protection. The court instructed the jury to consider: "Were they secrets. And, second, did the defendants slavishly use them or did they make up their own minds." These views are contrary to California law. "[D]efendants cannot escape responsibility by showing that they have improved upon or modified the plaintiff's process." *By-Buk Co.*, 163 Cal.App.2d at 169, 329 P.2d at 154, 118 USPQ at 554. The court observed in *Sinclair v. Aquarius Electronics, Inc.*, 42 Cal.App.3d 216, 222, 116 Cal.Rptr. 654, 659, 184 USPQ 682, 684 (1974) that minor variations are to be expected.

Suzuki argued to the jury, and repeats on appeal, that information that Richardson developed after issuance of the '332 patent, including the Alternate Shock Mount, is barred from trade secret status because it was generally disclosed in Richardson's patent or known to the general public, or because it merely implements the patented invention.

[24][25] The legal status of information and improvements made after a patent application has been filed is independent of the presence, or absence, of the patent application or ensuing patent. The information and improvements may be separately patentable; they may be preserved in confidence and disclosed only in accordance with agreement; and they are protected against misappropriation in accordance with the laws of contract and tort. The court misstated the law in telling the jury that the jury could decide whether Richardson could have both a valid patent and legal protection for later-developed information on the patented invention:

> So on the one hand [Richardson] says the ordinary person skilled in the art can take this patent and use it and make a machine based upon it. But, on the other hand, he says, however, the experimentation and the ability to do this constitutes trade secrets for which you must pay me. Now, that constitutes a dilemma and it's up to you to determine the extent to which Mr. Richardson may claim as trade secrets things that the ordinarily prudent person skilled in the art should be able to do on his own.

The district court's phrase "should be able to do on his own" may explain its misperception of the law. It is not known what Suzuki was able to do on its own, for Suzuki not only sought Richardson's knowhow, improvements, data, and information, but also agreed to respect the confidentiality thereof. This information is intellectual property in the eyes of the law, and is protected in accordance with law. *See generally* *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 493, 94 S.Ct. 1879, 1892, 40 L.Ed.2d 315 (1974). *See also* *Components for Research, Inc.*, 241 Cal.App.2d at 730, 50 Cal.Rptr. at 832 (whether the product design was patented or not, plaintiff is entitled to trade secret protection for manufacturing process); *Sinclair*, 42 Cal.App.3d at 225, 116 Cal.Rptr. at 660, 184 USPQ at 686 ("Trade secret law encourages invention in areas where patent law does not reach"). *Accord* *Thermotics, Inc. v. Bat-Jac Tool Co., Inc.*, 541 S.W.2d 255, 261, 193 USPQ 249, 253 (Tex.Civ.App.1976) (post-patent improvement protectable under trade secret law); *Franke v. Wiltschek*, 209 F.2d 493, 495, 99 USPQ 431, 433 (2d Cir.1953) (immaterial that defendants could have derived trade secrets from expired patent).

It is apparent that the court imposed a higher standard for trade secret status than is contained in California law. The court's instructions, commentary, and phrasing of the special verdicts not only placed a prejudicially heavy burden on Richardson, but also demeaned the information itself.

Despite this prejudicial environment, the jury found that items 5 and 6 were trade secrets and had been misappropriated by Suzuki, and assessed damages therefore. The jury also found that items 1-4 and 7-11 were not trade secrets, and that for some but not all of these items compensation***1245** should be awarded based on "benefit from the plaintiff's knowledge and from the time and effort expended by him".

The district court granted Suzuki's motion for a new trial with respect to items 5 and 6, and upheld the jury verdicts with respect to items 1-4 and 7-11.

C. The new trial of items 5 and 6

[26] The grant of a new trial is ordinarily not reviewable, but on this issue the district court entered final judgment for purposes of appeal, and certified three questions. The first certified question is:

> 1. Were the plaintiff's asserted trade secrets Nos. 5 and 6: (a) Actually valid proprietary trade secrets, as the jury found and awarded very substantial royalties; or (b) Did the plaintiff's contributions in these respects represent no more than the services of a skilled mechanic, which readily could have been duplicated by the defendant, and which entitled the plaintiff only to quantum meruit compensation, as the court believes; or (c) Were the plaintiff's contributions no more than those contemplated under the option agreement and paid

for by the defendant, as the defendant contends? We respond to this question: From the record before us the jury verdict that items 5 and 6 met the requirements for trade secret protection was supported by the great weight of the evidence. Richardson and Cazort testified about the design modifications that were the subject of item No. 5 and the Alternate Shock Mount subject of item No. 6. The Alternate Shock Mount was considered sufficiently novel and valuable that Suzuki included it in a patent application filed in Japan and later in the United States. The record does not negate the jury's determination of the value of this information. According to California law it is immaterial what Suzuki could have done, for it chose to use Richardson's information, which it obtained under restraint.

[27] In further response, we remark that the relation between the parties, set by contract, was a routine commercial arrangement wherein Richardson agreed to facilitate Suzuki's testing and evaluation of Richardson's invention. This did not convert Richardson's work in adapting his invention to Suzuki's motorcycle into the work of a hired technician whose work product was automatically owned by Suzuki. The proprietary nature of the work done and information provided by Richardson was established by agreement, as was the agreement that Suzuki would not use this information if it did not exercise its option.

There was substantial evidence before the jury that the information on items 5 and 6 was not publicly known, that Suzuki agreed to receive and preserve it in confidence, and that the information fully satisfies the statutory and jurisprudential requirements for protectible trade secrets.

In order to vacate the jury's verdict upholding items 5 and 6 as trade secrets and grant a new trial thereon, the trial court must find that the jury's verdict "is contrary to the clear weight of the evidence, or is based upon evidence which is false, or to prevent, in the sound discretion of the trial judge, a miscarriage of justice." *Hanson v. Shell Oil Co.*, 541 F.2d 1352, 1359 (9th Cir.1976), *cert. denied*, 429 U.S. 1074, 97 S.Ct. 813, 50 L.Ed.2d 792 (1977) (quoting *Moist Cold Refrigerator Co. v. Lou Johnson Co.*, 249 F.2d 246, 256, 115 USPQ 160, 168-69 (9th Cir.1957), *cert. denied*, 356 U.S. 968, 78 S.Ct. 1008, 2 L.Ed.2d 1074 (1958)); *William Inglis & Sons Baking Co. v ITT Continental Baking Co., Inc.*, 668 F.2d 1014, 1027 (9th Cir.1981), *cert. denied*, 459 U.S. 825, 103 S.Ct. 57, 74 L.Ed.2d 61 (1982). It is insufficient that the district court would simply have reached a different verdict.

Our review requires determination of whether the district court abused its discretion in its decision to grant the new trial. *Id. See Transgo, Inc. v. Ajac Transmission Parts Corp.*, 768 F.2d 1001, 1014, 227 USPQ 598, 602 (9th Cir.1985), *cert. denied*, 474 U.S. 1059, 106 S.Ct. 802, 88 L.Ed.2d 778 (1986) ("the grant or denial of either a motion for a new trial or a motion to amend the judgment must be reviewed on the basis of a determination of whether the district court abused its discretion.") ***1246** *See generally Seattle Box Co. v. Industrial Crating & Packing, Inc.*, 756 F.2d 1574, 1581, 225 USPQ 357, 363 (Fed.Cir.1985) ("Abuse of discretion may be established by showing that the district court either made an error of law, or a clear error of judgment, or made findings which were clearly erroneous.") The district court's statements, for example with respect to item 5, "I simply cannot conclude that that is a trade secret. It was an attempt to help Suzuki adapt the Richardson concept to the Suzuki machine ...", reflect an error of law.

Despite the legal error in the instructions, as we have discussed, any prejudice resulting therefrom favored Suzuki, not Richardson. We conclude that the district court exceeded its discretionary authority in vacating the jury verdict and ordering a new trial. That action is reversed, and the jury verdict is reinstated as to items Nos. 5 and 6, including the damages assessed for items Nos. 5 and 6.

D. Items 1-4 and 7-11

[28] For asserted trade secrets Nos. 1-4 and 7-11, the jury may well have been led by erroneous instructions into applying an incorrect legal standard, in finding that these items were not trade secrets. It appears, however, that Richardson did not move for judgment n.o.v. or a new trial on these verdicts. Although there is a hint in the post-trial colloquy that the court intended or was willing to retry all the trade secret issues along with items 5 and 6, this does not satisfy the rule, supported by logic, that the formalities of post-trial motions be respected. *Snellman v. Ricoh Co.*, 836 F.2d 528, 534, 5 USPQ2d 1341, 1346 (Fed.Cir.1987) (applying Ninth Circuit law in holding that motions for judgment n.o.v. and for a new trial must be made). Thus we have no authority to review these verdicts.

By special verdict the jury was also asked to assess damages for Suzuki's use of the information encompassed in each of items 1-4 and 7-11, even if

the information did not "rise to the dignity of trade secrets". The jury determined this sum for each item, some at $0, the highest at $25,000, for a total of $104,000. The district court sustained this award, on a theory of "quantum meruit compensation". Both parties appeal this award, Richardson asserting its inadequacy, and Suzuki arguing that Richardson was fully paid for his information in the option agreement, and is not entitled to damages for Suzuki's use of any information received from Richardson.

We have rejected, as a matter of law, Suzuki's theory that it is entitled to use, free, the information disclosed by Richardson under the option agreement. Richardson's disclosures were made under terms that prohibited their use by Suzuki if the option was not exercised. This contract provision does not depend on whether the information is a trade secret, but only on whether it was previously known to Suzuki or generally known to the public, as discussed *ante*.

[29] An appellate tribunal is abjured to determine whether a jury verdict can be sustained, on any reasonable theory. *Jaffke v. Dunham*, 352 U.S. 280, 281, 77 S.Ct. 307, 308, 1 L.Ed.2d 314 (1957) ("A successful party in the District Court may sustain its judgment on any ground that finds support in the record.")

[30] There was substantial evidence at trial whereby a reasonable jury could have determined the sums awarded by this jury. Indeed, Suzuki does not challenge the valuations of the damage awards for items 1-11, arguing instead that nothing at all is owing.

The judgment as to items 1-4 and 7-11 is affirmed, including damages assessed for these items in the total amount of $104,000.

V

Injunction

The district court, having entered final judgment that the Suzuki Full Floater suspension infringed claim 9 of the '332 patent, denied Richardson's motion for injunction.

Infringement having been established, it is contrary to the laws of property, of ***1247** which the patent law partakes, to deny the patentee's right to exclude others from use of his property. 35 U.S.C. § 261. "[T]he right to exclude recognized in a patent is but the essence of the concept of property". *Connell*, 722 F.2d at 1548, 220 USPQ at 198 (citing *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed.Cir.1983)).

[31][32] It is the general rule that an injunction will issue when infringement has been adjudged, absent a sound reason for denying it. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 842 F.2d 1275, 1281, 6 USPQ2d 1277, 1283 (Fed.Cir.1988). Suzuki has presented no such reason. This court stated in *H.H. Robertson Co. v. United Steel Deck, Inc.*, 820 F.2d 384, 390, 2 USPQ2d 1926, 1929-30 (Fed.Cir.1987), when reviewing an injunction granted *pendente lite:*

> In matters involving patent rights, irreparable harm has been presumed when a clear showing has been made of patent validity and infringement. *Smith International*, 718 F.2d at 1581, 219 USPQ at 692. This presumption derives in part from the finite term of the patent grant, for patent expiration is not suspended during litigation, and the passage of time can work irremediable harm.

We observe that the '332 patent will expire in less than four years, that litigation started over eight years ago, and that the district court remarked that further proceedings could consume "several years".

[33] Further, a misappropriator of trade secrets has no authorization of right to continue to reap the benefits of its wrongful acts. Richardson is entitled to an injunction against Suzuki's continuing use of trade secrets Nos. 5 and 6. *By-Buk Co.*, 163 Cal.App.2d at 167, 329 P.2d at 153, 118 USPQ at 553-54; *Components for Research, Inc.*, 241 Cal.App.2d at 730, 50 Cal.Rptr. at 832.

The denial of Richardson's request for injunction is reversed. On remand the district court shall enter appropriate injunctive relief.

VI

Fraud

The jury found by special verdicts that Suzuki fraudulently induced Richardson to reveal his trade secrets by concealing its intention not to exercise its option or take a license, and that Suzuki fraudulently concealed from Richardson the fact that it was developing the Full Floater "with the intention of declining to exercise the option and then nevertheless to utilize the plaintiff's trade secrets in the full floater". The jury also found fraud in that Suzuki filed the Tamaki patent application "in the knowledge that the invention asserted therein (the spring/swing arm connection) was first disclosed to them by Richardson". The jury awarded Richardson $20,000 in compensatory and $100,000 in punitive damages.

The district court vacated the judgment and ordered a new trial. Suzuki asserts that the court should have granted Suzuki's motion for judgment n.o.v. instead of ordering a new trial, while Richardson asserts that the court should have upheld the jury verdicts.

The district court certified the question of how to treat its belief that Suzuki did not commit the offenses of fraud and concealment found by the jury, including the question of punitive damages. We first must consider whether a reasonable jury could have reached the verdicts here reached. *Lavender v. Kurn*, 327 U.S. at 653, 66 S.Ct. at 744. Apt is the statement of the Ninth Circuit in *Crocker-Citizens Nat'l Bank v. Control Metals Corp.*, 566 F.2d 631, 635 (9th Cir.1977): "Courts are not free to reweigh the evidence and set aside the jury verdict merely because the jury could have drawn different inferences or conclusions or because judges feel that other results are more reasonable", quoting *Cockrum v. Whitney*, 479 F.2d 84, 86 (9th Cir.1973), in turn quoting *Tennant v. Peoria & P.U. Ry. Co.*, 321 U.S. 29, 35, 64 S.Ct. 409, 412, 88 L.Ed. 520 (1944).

[34][35] The record shows that there was testimony, based on certain of Suzuki's documents, on which a reasonable jury ***1248** could have supported these verdicts. There were issues of credibility, and inferences that could reasonably have been drawn in a manner adverse to Suzuki. "The credibility of witnesses and the weight of the evidence are issues for the jury and are generally not subject to appellate review." *Benigni*, 853 F.2d at 1525. While the district court may have believed that Suzuki did not commit fraud, review shows that the requirements for vacating the jury verdicts and relitigating the issue were not met. *Hanson*, 541 F.2d at 1359; *William Inglis*, 668 F.2d at 1027. A fresh trial is not warranted simply because the district court would have reached a different verdict.

[36] A jury assessment of punitive damages is not excluded in circumstances such as those here presented, where the jury expressly found fraud. *Tri-Tron Int'l v. Velto*, 525 F.2d 432, 437, 188 USPQ 177, 181 (9th Cir.1975) ("where compensatory damages are sought and awarded, the court has power, on a proper record, to award punitive damages"), citing *Clark v. Bunker*, 453 F.2d 1006, 1012, 172 USPQ 420, 424 (9th Cir.1972), in turn citing *El Rancho, Inc. v. First Nat'l Bank*, 406 F.2d 1205, 1218 (9th Cir.1968), *cert. denied*, 396 U.S. 875, 90 S.Ct. 150, 24 L.Ed.2d 133 (1969) (jury verdict awarding punitive damages was supported by evidence of malice) and *Davenport v. Mutual Benefit Health & Accident Ass'n*, 325 F.2d 785, 787 (9th Cir.1963) (remand for trial to allow evidence of fraud to support claim of punitive damages.)

The district court correctly instructed the jury as to the law, stating that "it's only if you find that the defendants' conduct stem from malice, oppression, fraud or bad faith that you can find any punitive damage at all." As stated in *In re Innovative Construction Systems, Inc.*, 793 F.2d 875, 889, 230 USPQ 94, 104 (7th Cir.1986):

> [A] breach of faith underlies every trade secret claim. However, establishing that breach alone is insufficient to warrant an award of punitive damages; one must also demonstrate that the defendant acted wantonly, willfully, or in reckless disregard of the plaintiff's rights. (Citations omitted)

See also Neal v. Farmers Insurance Exchange, 21 Cal.3d 910, 928, 582 P.2d 980, 986, 148 Cal.Rptr. 389, 395 (1978) ("In order to justify an award of exemplary damages, the defendant must be guilty of oppression, fraud or malice. (Civ.Code § 3294.) He must act with the intent to vex, injure or annoy, or with a conscious disregard of the plaintiff's rights") (quoting *Silberg v. California Life Insurance Co.*, 11 Cal.3d 452, 462, 521 P.2d 1103, 1110, 113 Cal.Rptr. 711, 718 (1974)); *Reynolds Metals Co. v. Lampert*, 316 F.2d 272, 275 (9th Cir.1963), *cert. denied*, 376 U.S. 910, 84 S.Ct. 664, 11 L.Ed.2d 608 (1964) (in jury trial, evidence to justify punitive damages must show injury was done maliciously or willfully and wantonly or committed with bad motive or recklessly); *Transgo, Inc.*, 768 F.2d at 1024 (The determination to award punitive damages was "within the exclusive province of the jury") (quotingRunge v. Lee, 441 F.2d 579, 584, 169 USPQ 388, 392 (9th Cir.), *cert. denied*, 404 U.S. 887, 92 S.Ct. 197, 30 L.Ed.2d 169 (1971)).

The jury having found by special verdicts that Suzuki acted fraudulently, the requisite intent was established. "We give the trial judge and jury wide discretion in assessing punitive damages." *Hatrock v. Edward D. Jones & Co.*, 750 F.2d 767, 772 (9th Cir.1984). The jury's award was not "so disproportionate to the damages sustained as to be the result of passion or prejudice". *Id.* (citing *Neal*, 21 Cal.3d at 928, 582 P.2d at 990, 148 Cal.Rptr. at 399). *Transgo, Inc.*, 768 F.2d at 1024 ("We will not overturn such an award unless it appears that the jury was influenced by passion or prejudice.") (citing *Harmsen v. Smith*, 693 F.2d 932, 947 (9th Cir.1982), *cert. denied*, 464 U.S. 822, 104 S.Ct. 89, 78 L.Ed.2d 97 (1983)).

We answer the certified question that, in this case, neither a new trial nor judgment n.o.v. was warranted. The order of a new trial on this issue is vacated. The judgment on the jury verdicts of fraud and the award of compensatory and punitive damages is reinstated.

***1249** VII

The Tamaki Patent

Richardson states that Suzuki fraudulently patented the Alternate Shock Mount that had been disclosed to Suzuki by Richardson and Cazort, in a patent that also described the "criss-cross" modification developed at Suzuki. There was evidence and argument on the factual premises, including the absence of supporting documentation on the part of the named inventors Hirohide Tamaki and Manabu Suzuki, the earliest record on their behalf being dated October 1979. The corresponding Japanese patent application was filed on October 16, 1979.

The jury rendered the following special verdicts:

C-3. Did Suzuki and/or Mr. Tamaki file the Tamaki patent application in the knowledge that the invention asserted therein (the spring/swing arm connection) was first disclosed to them by Richardson:

Answer: YES

H-1. Do you find that the Plaintiff, Richardson, is the real inventor of the invention shown in the Tamaki patents and patent applications?

Answer: NO

It was not significantly disputed at trial that claims 1 through 8 of the Tamaki corresponding United States Patent No. 4,457,393 cover the Alternate Shock Mount of Richardson and Cazort, and that claim 9 includes the criss-cross embodiment of Tamaki and Suzuki. (The scope of claim 5 is raised, but is not material to our conclusion.)

[37] The district court denied Richardson's post-trial motion that the Tamaki patent be assigned to Richardson. In colloquy with counsel the court explained that it could not do so because "the jury said Richardson wasn't the inventor". Indeed it was conceded, and discussed at trial, that Richardson and Cazort, not Richardson alone, invented the Alternate Shock Mount. Cazort, as well as Richardson, testified at length on this structure. Special verdict H-1 that Richardson is not "the real inventor" is in accord with the co-inventor status of Cazort, and also with the Japanese contribution of the criss-cross embodiment.

The force of special verdict C-3 is not diminished. This verdict was not challenged on appeal. "It was further the duty of the court to direct the appropriate judgment to be entered upon the special verdict." *Traders and General Insurance Co. v. Mallitz*, 315 F.2d 171, 175 (5th Cir.1963). The district court having failed to implement this verdict, Richardson's motion for judgment and for assignment of the Tamaki patents was not out of order.

[38] The remedy of assignment of the Tamaki patents is a different question from whether Richardson is a sole or joint inventor. The correction of inventorship is an administrative step, and is not before the court. Similarly, the presence of a further modification in one or two claims of the patent directed to the Alternate Shock Mount does not negate the imposition of an equitable remedy. To hold otherwise would ratify and indeed reward the wrongdoing.

Based on the jury verdict, Richardson is entitled to ownership of the patents as against Suzuki. Such remedy is appropriate under the circumstances; *see, e.g., Colgate-Palmolive Co. v. Carter Products, Inc.*, 230 F.2d 855, 865, 108 USPQ 383, 391 (4th Cir.), *cert. denied*, 352 U.S. 843, 77 S.Ct. 43, 1 L.Ed.2d 59 (1956) (corporate assignee of patent application ordered to assign to original holder of trade secrets all rights to patent applications based thereon); *De Long Corp. v. Lucas*, 176 F.Supp. 104, 134 (S.D.N.Y.1959), *aff'd*, 278 F.2d 804 (2nd Cir.), *cert. denied*, 364 U.S. 833, 81 S.Ct. 71, 5 L.Ed.2d 58 (1960) (when an employee has acquired patents on inventions developed by his former employer, "the courts will hold the wrongdoer to be a constructive trustee of the property misappropriated and will order a conveyance by the wrongdoer to the former employer"); *Becher v. Contoure Laboratories, Inc.*, 279 U.S. 388, 49 S.Ct. 356, 73 L.Ed.2d 752 (1929) (same); *Saco-Lowell Shops v. Reynolds*, 141 F.2d 587, 598, 61 USPQ 3, 13 (4th Cir.1944) (requiring assignment of patent ***1250** based on ideas received by licensee from licensor in confidence during development of invention for market).

[39] Suzuki argues that Richardson has no remedy other than by seeking an interference in the United States Patent and Trademark Office with his own invention, and presumably by taking similar actions, if such are available, in other countries. We do not agree. The courts are not powerless to redress wrongful appropriation of intellectual property by those subject to the courts' jurisdiction.

The denial of Richardson's motion for judgment is reversed. Suzuki shall assign to Richardson the patents filed by Suzuki that include the Richardson/Cazort invention of the Alternate Shock Mount, in all countries. We remand to the district court for the purpose of implementing compliance.

VIII

Prejudgment Interest

The district court denied Richardson's request for prejudgment interest on both the patent infringement and the trade secret damage awards. Prejudgment interest is the rule governing this class of award. *General Motors Corp. v. Devex Corp.*, 461 U.S. 648, 655, 103 S.Ct. 2058, 2062, 76 L.Ed.2d 211, 217 USPQ 1185, 1188 (1983); *Lummus Industries, Inc. v. D.M. & E. Corp.*, 862 F.2d 267, 274, 8 USPQ2d 1983, 1988 (Fed.Cir.1988); *Fromson*, 853 F.2d at 1573-74, 7 USPQ2d at 1611; *Bio-Rad Laboratories, Inc. v. Nicolet Instrument Corp.*, 807 F.2d 964, 967, 1 USPQ2d 1191, 1193 (Fed.Cir.1986), *cert. denied*, 482 U.S. 915, 107 S.Ct. 3187, 96 L.Ed.2d 675 (1987).

No exceptional circumstances having been shown, and no reason why damages for misappropriated trade secrets should be treated differently from damages for patent infringement, the denial of prejudgment interest is reversed.

IX

Willful Infringement and Exceptional Case

The district court refused to submit the question of willful infringement to the jury, stating that Richardson had not provided sufficient evidence to go to the jury.

To refuse to give an issue to the jury is to direct a verdict in favor of the opposing party. Thus we review the district court's ruling on the standard of "whether the evidence permits only one reasonable conclusion after viewing the evidence in the light most favorable to the non-moving party and drawing all inferences in favor of that party." *Bulgo v. Munoz*, 853 F.2d 710, 714 (9th Cir.1988) (citing *Peterson v. Kennedy*, 771 F.2d 1244, 1256 (9th Cir.1985), *cert. denied*, 475 U.S. 1122, 106 S.Ct. 1642, 90 L.Ed.2d 187 (1986)). *See also Connell*, 722 F.2d at 1546, 220 USPQ at 197.

[40] Richardson refers to the evidence adduced in connection with the jury verdicts of fraud, to the verdicts of misappropriation of trade secrets 5 and 6, to the absence of any opinion of United States counsel concerning validity of the '332 patent when Suzuki started its infringing activity, and to evidence from Suzuki's records tending to show bad faith. Viewing this evidence in the light most favorable to Richardson, and drawing all reasonable inferences in his favor, there was sufficient evidence to take to the jury, for the evidence does not require a verdict in favor of Suzuki. Absent sufficient basis for directing the verdict, Richardson has the right of jury determination of this factual question. Willfulness of behavior is a classical jury question of intent. *Shiley*, 794 F.2d at 1568, 230 USPQ at 115; *Hammerquist v. Clarke's Sheet Metal, Inc.*, 658 F.2d 1319, 1325-26, 212 USPQ 481, 486 (9th Cir.1981), *cert. denied*, 460 U.S. 1052, 103 S.Ct. 1499, 75 L.Ed.2d 930 (1983). When trial is had to a jury, the issue should be decided by the jury.

We remand for this purpose. The jury's findings on the issue of willfulness will be pertinent not only to the question of multiplication of damages under 35 U.S.C. § 284, but also to determination of whether this is an exceptional case in terms of 35 U.S.C. § 285. Entitlement under ***1251** California Civil Code § 3426 et seq. may also be considered.

X

Other Arguments

Both sides have raised many points in their briefs, disputing most aspects of the proceedings. We have considered all arguments in reaching our conclusions.

Costs

The award by the trial court of only one third costs to Richardson, in view of the judgments in his favor on the major substantive issues, exceeded the trial court's discretionary authority. Richardson is entitled to his statutory costs incurred before the district court. The reduction thereof is reversed.

Costs on this appeal are taxed in favor of Richardson.

AFFIRMED IN PART, REVERSED IN PART, VACATED IN PART, AND REMANDED

868 F.2d 1226, 9 U.S.P.Q.2d 1913

Briefs and Other Related Documents (Back to top)

• 1988 WL 1045329 (Appellate Brief) Reply Brief for Cross Appellants (May. 15, 1988)Original Image of this Document (PDF)

• 1988 WL 1045328 (Appellate Brief) Corrected Appellant's Reply Brief (Apr. 20, 1988)Original Image of this Document (PDF)

• 1988 WL 1045326 (Appellate Brief) Brief for Cross Appellants (Mar. 14, 1988)Original Image of this Document (PDF)

• 1988 WL 1045327 (Appellate Brief) Corrected Appellant's Opening Brief (Feb. 01, 1988)Original Image of this Document (PDF)

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Briefs and Other Related Documents

United States Court of Appeals,
Federal Circuit.
VERDEGAAL BROTHERS, INC., William Verdegaal, George Verdegaal, Appellees,
v.
UNION OIL COMPANY OF CALIFORNIA, Brea Agricultural Services, Inc., Appellants.
Appeal No. 86-1258.

March 12, 1987.

Action was instituted for alleged patent infringement. The United States District Court for the Eastern District of California, Robert E. Coyle, J., entered judgment on verdict for plaintiff, declaring patent valid and infringed, and defendants appealed. The Court of Appeals, Nies, Circuit Judge, held that patent relating to a process for making urea-sulfuric acid liquid fertilizer by reacting water, urea, a nitrogen-containing chemical, and sulferic acid, a sulfur-containing chemical, in particular proportions was anticipated by prior art reference disclosing processes for making both urea-phosphoric acid and urea-sulferic acid fertilizers and was invalid.

Reversed.

See also, Fed.Cir., 750 F.2d 947.

West Headnotes

[1] Federal Civil Procedure 2609
170Ak2609 Most Cited Cases
A district court presented with a motion for judgment notwithstanding the verdict should consider all of the evidence, in a light most favorable to nonmoving party, drawing all reasonable inferences favorable to that party, without determining credibility of witnesses, and without substituting its choice for that of the jury and deciding between conflicting elements of the evidence, and should grant the motion only when it is convinced upon the record before the jury that reasonable persons could not have reached a verdict for
the nonmoving party. 35 U.S.C.A. § § 102, 103; Fed.Rules Civ.Proc.Rule 50(a, b), 28 U.S.C.A.

[2] Federal Civil Procedure 2608.1
170Ak2608.1 Most Cited Cases
(Formerly 170Ak2608)
Party moving for judgment notwithstanding the verdict must show that either the jury's factual findings are not supported by substantial evidence, or, if they are, that those findings cannot support the legal conclusions which necessarily were drawn by the jury and forming its verdict. 35 U.S.C.A. § § 102, 103; Fed.Rules Civ.Proc.Rule 50(a, b), 28 U.S.C.A.

[3] Patents 36(2)
291k36(2) Most Cited Cases
Presumption of validity afforded a patent requires that party challenging validity prove facts establishing invalidity by clear and convincing evidence. 35 U.S.C.A. § 282.

[4] Patents 72(1)
291k72(1) Most Cited Cases
A claim is anticipated only if each and every element as set forth in claim is found, either expressly or inherently described, in a single prior art reference. 35 U.S.C.A. § 102(e).

[5] Patents 66(1.12)
291k66(1.12) Most Cited Cases
Preparations.
Patent relating to a process for making urea-sulfuric acid liquid fertilizer by reacting water, urea, a nitrogen-containing chemical, and sulfuric acid, a sulfur-containing chemical, in particular proportions was anticipated by prior art reference disclosing processes for making both urea-phosphoric acid and urea-sulfuric acid fertilizers and was invalid. 35 U.S.C.A. § § 102(e), 282.

[6] Patents 72(1)
291k72(1) Most Cited Cases
It was inappropriate for holder of patented fertilizer process to rely on fact that sulfuric acid was added slowly in prior art reference, whereas claimed process allowed for rapid addition, where there was no limitation in subject process with respect to rate at which sulfuric acid was added. 35 U.S.C.A. § § 102(e), 282.

[7] Patents 62(1)
291k62(1) Most Cited Cases
Discarding testimony of experts with respect to what

prior art reference taught did not eliminate reference itself as evidence or its uncontradicted disclosure that a base of recycled fertilizer in a process could be used to make more of the product and, hence, did not preclude conclusion that claimed process for making liquid fertilizer was invalid as anticipated by prior art. 35 U.S.C.A. § § 102(e), 282.

[8] **Patents** 72(1)
291k72(1) Most Cited Cases
Failure of prior art reference to explicitly identify heel in process for manufacturing liquid fertilizer as a heat sink did not preclude reference from anticipating claimed process, thus requiring a finding of invalidity, where fact that heel functioned as a heat sink was inherent in prior art reference. 35 U.S.C.A. § § 102(e), 282.

Patents 328(2)
291k328(2) Most Cited Cases
4,310,343. Declared invalid as anticipated by prior art.

Patents 328(2)
291k328(2) Most Cited Cases
4,315,763. Prior art.
***629** Andrew J. Belansky, Christie, Parker & Hale, Pasadena, Cal., argued for appellants. ***630** With him on the brief was David A. Dillard.

John P. Sutton, Limbach, Limbach & Sutton, San Francisco, Cal., argued for appellees. With him on the brief was Michael E. Dergosits.

Before MARKEY, Chief Judge, and DAVIS and NIES, Circuit Judges.

NIES, Circuit Judge.

Union Oil Company of California and Brea Agricultural Services, Inc. (collectively Union Oil) appeal from a judgment of the United States District Court for the Eastern District of California, No. CV-F-83-68 REC, entered on a jury verdict which declared U.S. Patent No. 4,310,343 ('343), owned by Verdegaal Brothers, Inc., "valid" and claims 1, 2, and 4 thereof infringed by Union Oil. Union Oil's motion for judgment notwithstanding the verdict (JNOV) was denied. We reverse.

I
BACKGROUND

The General Technology

The patent in suit relates to a process for making certain known urea-sulfuric acid liquid fertilizer products. These products are made by reacting water, urea (a nitrogen-containing chemical), and sulfuric acid (a sulfur-containing chemical) in particular proportions. The nomenclature commonly used by the fertilizer industry refers to these fertilizer products numerically according to the percentages by weight of four fertilizer constituents in the following order: nitrogen, phosphorous, potassium, and sulfur. Thus, for example, a fertilizer containing 28% nitrogen, no phosphorous or potassium, and 9% sulfur is expressed numerically as 28-0-0-9.

The Process of the '343 Patent

The process disclosed in the '343 patent involves the chemical reaction between urea and sulfuric acid, which is referred to as an exothermic reaction because it gives off heat. To prevent high temperature buildup, the reaction is conducted in the presence of a nonreactive, nutritive heat sink which will absorb the heat of reaction. Specifically, a previously-made batch of liquid fertilizer--known as a "heel"--can serve as the heat sink to which more reactants are added. Claims 1 and 2 are representative:

1. In a process for making a concentrated liquid fertilizer by reacting sulfuric acid and urea, to form an end product, the improvement comprising:
a. providing a non-reactive, nutritive heat sink, capable of dissipating the heat of urea and sulfuric acid, in an amount at least 5% of the end product,
b. adding water to the heat sink in an amount not greater than 15% of the end product,
c. adding urea to the mixture in an amount of at least 50% of the total weight of the end product,
d. adding concentrated sulfuric acid in an amount equal to at least 10% of the total weight of the end product.
2. The process of claim 1 wherein the heat sink is recycled liquid fertilizer.

Procedural History

Verdegaal brought suit against Union Oil in the United States District Court for the Eastern District of California charging that certain processes employed by Union Oil for making liquid fertilizer products infringed all claims of its '343 patent. Union Oil defended on the grounds of noninfringement and patent invalidity under 35 U.S.C. § § 102, 103. The action was tried before a jury which returned a verdict consisting of answers to five questions. Pertinent here are its answers that the '343 patent was "valid" over the prior art, and that certain of Union Oil's processes infringed claims 1, 2, and 4 of the patent. None were found to infringe

claims 3 or 5. Based on the jury's verdict, the district court entered judgment in favor of Verdegaal.

Having unsuccessfully moved for a directed verdict under Fed.R.Civ.P. 50(a), Union Oil timely filed a motion under Rule 50(b) for JNOV seeking a judgment that the claims of the '343 patent were invalid ***631** under sections 102 and 103. The district court denied the motion without opinion.

II
ISSUE PRESENTED

Did the district court err in denying Union Oil's motion for JNOV with respect to the validity of claims 1, 2, and 4 of the '343 patent?

III
Standard of Review

[1] When considering a motion for JNOV a district court must: (1) consider all of the evidence; (2) in a light most favorable to the non-moving party; (3) drawing all reasonable inferences favorable to that party; (4) without determining credibility of the witnesses; and (5) without substituting its choice for that of the jury's in deciding between conflicting elements of the evidence. *Railroad Dynamics, Inc. v. A. Stucki Co.*, 727 F.2d 1506, 1512-13, 220 USPQ 929, 936 (Fed.Cir.), *cert. denied*, 469 U.S. 871, 105 S.Ct. 220, 83 L.Ed.2d 150 (1984); *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1546, 220 USPQ 193, 197 (Fed.Cir.1983). A district court should grant a motion for JNOV only when it is convinced upon the record before the jury that reasonable persons could not have reached a verdict for the nonmoving party. *Railroad Dynamics*, 727 F.2d at 1513, 220 USPQ at 936; *Connell*, 722 F.2d at 1546, 220 USPQ at 197.

[2] To reverse the district court's denial of the motion for JNOV, Union Oil must convince us that either the jury's factual findings are not supported by substantial evidence, or, if they are, that those findings cannot support the legal conclusions which necessarily were drawn by the jury in forming its verdict. *See Perkin-Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 893, 221 USPQ 669, 673 (Fed.Cir.), *cert. denied*, 469 U.S. 857, 105 S.Ct. 187, 83 L.Ed.2d 120 (1984); *Railroad Dynamics*, 727 F.2d at 1512, 220 USPQ at 936. Substantial evidence is more than just a mere scintilla; it is such relevant evidence from the record taken as a whole as a reasonable mind might accept as adequate to support the finding under review. *Consolidated Edison Co. v. NLRB*, 305 U.S. 197, 229, 59 S.Ct. 206, 216, 83 L.Ed. 126 (1938); *Perkin-Elmer*, 732 F.2d at 893, 221 USPQ at 673; *SSIH Equip. S.A. v. U.S. Int'l Trade Comm'n*, 718 F.2d 365, 371 n. 10, 218 USPQ 678, 684 n. 10 (Fed.Cir.1983). A trial court's denial of a motion for JNOV must stand unless the evidence is of such quality and weight that reasonable and fair-minded persons in the exercise of impartial judgment could not reasonably return the jury's verdict. *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758, 221 USPQ 473, 477 (Fed.Cir.1984).

[3] Our precedent holds that the presumption of validity afforded a U.S. patent by 35 U.S.C. § 282 requires that the party challenging validity prove the facts establishing invalidity by clear and convincing evidence. *American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1360, 220 USPQ 763, 770 (Fed.Cir.), *cert. denied*, 469 U.S. 821, 105 S.Ct. 95, 83 L.Ed.2d 41 (1984). Thus, the precise question to be resolved in this case is whether Union Oil's evidence is so clear and convincing that reasonable jurors could only conclude that the claims in issue were invalid. *See Perkin-Elmer*, 732 F.2d at 893, 221 USPQ at 673; *Railroad Dynamics*, 727 F.2d at 1511, 220 USPQ at 935.

Anticipation

[4] A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *See, e.g., Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 715, 223 USPQ 1264, 1270 (Fed.Cir.1984); *Connell*, 722 F.2d at 1548, 220 USPQ at 198; *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 771, 218 USPQ 781, 789 (Fed.Cir.1983), *cert. denied*, 465 U.S. 1026, 104 S.Ct. 1284, 79 L.Ed.2d 687 (1984). Union Oil asserts that the subject claims of the '343 patent ***632** are anticipated under 35 U.S.C. § 102(e) [FN1] by the teachings found in the original application for U.S. Patent No. 4,315,763 to Stoller, which the jury was instructed was prior art.

> FN1. Section 102(e) provides:
> A person shall be entitled to a patent unless-
> ....
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent....

[5] From the jury's verdict of patent validity, we must presume that the jury concluded that Union Oil failed to prove by clear and convincing evidence that claims 1, 2, and 4 were anticipated by the Stoller patent. *See Perkin-Elmer*, 732 F.2d at 893, 221 USPQ at 673; *Railroad Dynamics*, 727 F.2d at 1516, 220 USPQ at 939. Under the instructions of this case, this conclusion could have been reached only if the jury found that the Stoller patent did not disclose each and every element of the claimed inventions. Having reviewed the evidence, we conclude that substantial evidence does not support the jury's verdict, and, therefore, Union Oil's motion for JNOV on the grounds that the claims were anticipated should have been granted.

The Stoller patent discloses processes for making both urea-phosphoric acid and urea-sulfuric acid fertilizers. Example 8 of Stoller specifically details a process for making 30-0-0-10 urea-sulfuric acid products. There is no dispute that Example 8 meets elements b, c, and d of claim 1, specifically the steps of adding water in an amount not greater than 15% of the product, urea in an amount of at least 50% of the product, and concentrated sulfuric acid in an amount of at least 10% of the product. Verdegaal disputes that Stoller teaches element a, the step of claim 1 of "providing a non-reactive, nutritive heat sink." As set forth in claim 2, the heat sink is recycled fertilizer. [FN2]

> FN2. Claim 4 is written in terms of approximate percentages of all reactants by weight of the end product. No argument is made that the process of claim 4 would result in a fertilizer product any different from that disclosed by Example 8 of Stoller.

The Stoller specification, beginning at column 7, line 30, discloses:

> Once a batch of liquid product has been made, it can be used as a base for further manufacture. This is done by placing the liquid in a stirred vessel of appropriate size, adding urea in sufficient quantity to double the size of the finished batch, adding any water required for the formulation, and slowly adding the sulfuric acid while stirring. Leaving a heel of liquid in the vessel permits further manufacture to be conducted in a stirred fluid mass.

This portion of the Stoller specification explicitly teaches that urea and sulfuric acid can be added to recycled fertilizer, i.e., a heel or base of previously-made product. Dr. Young, Union Oil's expert, so testified. Verdegaal presented no evidence to the contrary.

[6] Verdegaal first argues that Stoller does not anticipate because in Stoller's method sulfuric acid is added *slowly*, whereas the claimed process allows for rapid addition. However, there is no limitation in the subject claims with respect to the rate at which sulfuric acid is added, and, therefore, it is inappropriate for Verdegaal to rely on that distinction. *See SSIH*, 718 F.2d at 378, 218 USPQ at 689. It must be assumed that slow addition would not change the claimed process in any respect including the function of the recycled material as a heat sink.

[7] Verdegaal next argues that the testimony of Union Oil's experts with respect to what Stoller teaches could well have been discounted by the jury for bias. Discarding that testimony does not eliminate the reference itself as evidence or its uncontradicted disclosure that a base of recycled fertilizer in a process may be used to make more of the product.

[8] Verdegaal raises several variations of an argument, all of which focus on the ***633** failure of Stoller to explicitly identify the heel in his process as a "heat sink." In essence, Verdegaal maintains that because Stoller did not recognize the "inventive concept" that the heel functioned as a heat sink, Stoller's process cannot anticipate. This argument is wrong as a matter of fact and law. Verdegaal's own expert, Dr. Bahme, admitted that Stoller discussed the problem of high temperature caused by the exothermic reaction, and that the heel could function as a heat sink. [FN3] In any event, Union Oil's burden of proof was limited to establishing that Stoller disclosed the same process. It did not have the additional burden of proving that Stoller recognized the heat sink capabilities of using a heel. Even assuming Stoller did not recognize that the heel of his process functioned as a heat sink, that property was inherently possessed by the heel in his disclosed process, and, thus, his process anticipates the claimed invention. *See In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981); *In re Swinehart*, 439 F.2d 210, 212-13, 169 USPQ 226, 229 (CCPA 1971). The pertinent issues are whether Stoller discloses the process of adding urea and sulfuric acid to a previously-made batch of product, and whether that base would in fact act as a heat sink. On the entirety of the record, these issues could only be resolved in the affirmative.

> FN3. There is no dispute that the percentage of heel described in Stoller meets the percentage of heat sink required by the claims.

On appeal Verdegaal improperly attempts to attack the status of the Stoller patent as prior art, stating in its brief:

> Verdegaal also introduced evidence at trial that the Stoller patent is not prior art under 35 U.S.C. § § 102(e)/103. Professor Chisum testified that the Stoller patent, in his opinion, was not prior art.... This conclusion finds support in *In re Wertheim*, 646 F.2d 527 (CCPA 1981), and 1 Chisum on Patents § 3.07[3].

Appellee Brief at 27 (record cite omitted). Seldom have we encountered such blatant distortion of the record. A question about the status of the Stoller disclosure as prior art did arise at trial. Union Oil asserted that, even though the Stoller patent issued after the '343 patent, Stoller was prior art under section 102(e) as of its filing date which was well before the filing date of Verdegaal's application. Professor Chisum never testified that the Stoller patent was *not* prior art, but rather, stated that *he did not know* whether it was prior art. An excerpt from the pertinent testimony leaves no doubt on this point:

> Q. (Mr. Sutton): And do you know whether the Stoller patent is prior art to the application of the Verdegaal patent?
> A. (Prof. Chisum): I don't know that it is, no.

We find it even more incredible that Verdegaal would attempt to raise an issue with respect to the status of the Stoller patent given that the case was submitted to the jury with the instruction that the original Stoller patent application was prior art. [FN4] Verdegaal made no objection to that instruction below, and in its appeal briefs, the instruction is cavalierly ignored.

> FN4. The jury instruction read:
> Stoller filed two patent applications--an original application on October 30th, 1978, and a second on February 7th, 1980. Under the patent laws, the claims of the 343 patent are invalid if you find that the original application (Exhibit BL) anticipates the process claimed in the 343 patent.

In sum, Verdegaal is precluded from arguing that the Stoller patent should not be considered prior art. *See* Fed.R.Civ.P. 51; *Weinar v. Rollform Inc.*, 744 F.2d 797, 808, 223 USPQ 369, 375 (Fed.Cir.1984), *cert. denied*, 470 U.S. 1084, 105 S.Ct. 1844, 85 L.Ed.2d 143 (1985); *Bio-Rad Laboratories, Inc. v. Nicolet Instrument Corp.*, 739 F.2d 604, 615, 222 USPQ 654, 662 (Fed.Cir.), *cert. denied*, 469 U.S. 1038, 105 S.Ct. 516, 83 L.Ed.2d 405 (1984). [FN5]

> FN5. Union Oil also argues that Verdegaal's counsel misled the jury by its closing rebuttal argument:
> [B]ut I think it's important to keep in mind that [Stoller] couldn't have been a prior patent because it issued a month after the Verdegaal patent had issued.
> We disapprove of Verdegaal's tactic which would form the basis for a grant of a motion for a new trial but for our conclusion that outright reversal of the ruling on the motion for JNOV is in order.

***634** After considering the record taken as a whole, we are convinced that Union Oil established anticipation of claims 1, 2, and 4 by clear and convincing evidence and that no reasonable juror could find otherwise. Consequently, the jury's verdict on validity is unsupported by substantial evidence and cannot stand. Thus, the district court's denial of Union Oil's motion for JNOV must be reversed.

Conclusion

Because the issues discussed above are dispositive of this case, we do not find it necessary to reach the other issues raised by Union Oil. [FN6] In accordance with this opinion, we reverse the portion of the judgment entered on the jury verdict upholding claims 1, 2, and 4 of the '343 patent as valid under section 102(e) and infringed.

> FN6. It should not be inferred that all of these issues were properly before us. Union Oil appears to assume that on appeal it may dispute the resolution of any *issue* which is denominated an "issue of law" even though it was not raised in its motion for JNOV. This is incorrect. *See Railroad Dynamics*, 727 F.2d at 1511, 220 USPQ at 934.

REVERSED.

814 F.2d 628, 2 U.S.P.Q.2d 1051

Briefs and Other Related Documents (Back to top)

• 1986 WL 732841 (Appellate Brief) Reply Brief for Appellants (Sep. 08, 1986)Original Image of this Document with Appendix (PDF)

• 1986 WL 732840 (Appellate Brief) Brief for Appellees (Aug. 22, 1986)Original Image of this Document (PDF)

• 1986 WL 732839 (Appellate Brief) Brief for Appellants (Jul. 14, 1986)Original Image of this Document with Appendix (PDF)

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